Mayo Clinic Cancer Center

Phase II Study of Short Course Hypofractionated Proton Beam Therapy incorporating 18F-DOPA-PET/MRI for Elderly Patients with Newly Diagnosed Glioblastoma

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

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Drug Availability

Supplied Investigational Agents:

Arizona ^{18}F-DOPA IND#: 140882

Rochester ^{18}F-DOPA IND#: 61300

Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	Rad Onc Study Coordinator [redacted]
Protocol document, consent form, regulatory issues	See Protocol Catalog for current Research Protocol Specialist Assigned: [redacted]
Arizona ^{18}F-DOPA IND	[redacted]
Serious Adverse Event Reporting	[redacted]

*No waivers of eligibility allowed

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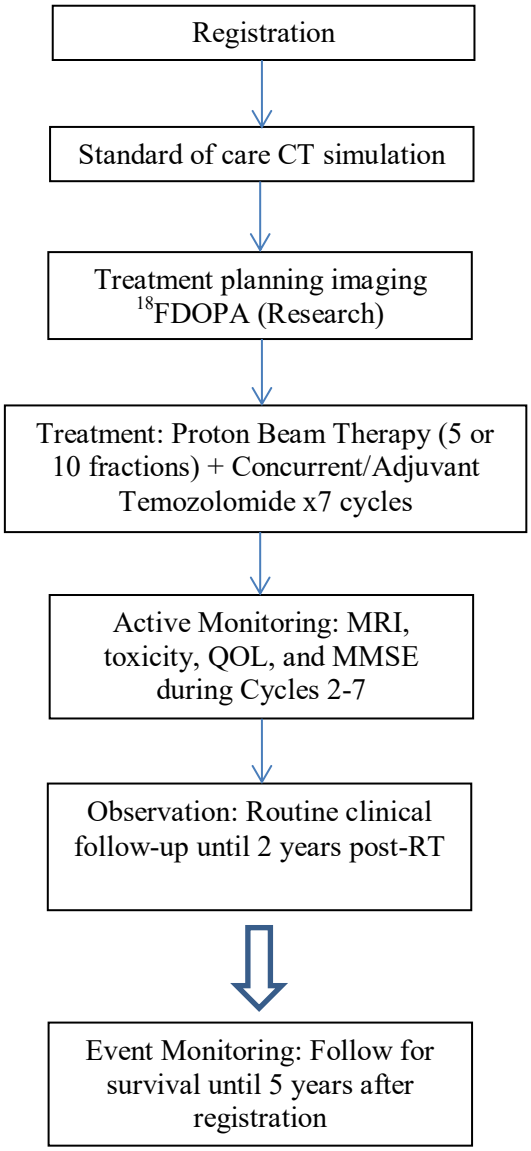
Schema


Registration
Standard of care CT simulation
Treatment planning imaging
18FDOPA (Research)
Treatment: Proton Beam Therapy (5 or 10 fractions) + Concurrent/Adjuvant Temozolomide x7 cycles
Active Monitoring: MRI, toxicity, QOL, and MMSE during Cycles 2-7
Observation: Routine clinical follow-up until 2 years post-RT
Event Monitoring: Follow for survival until 5 years after registration

1.0 Background

Glioblastoma Multiforme (GBM) is the most common primary malignant brain tumor with approximately 11000 cases yearly. From this group, approximately 50% of all newly diagnosed patients are older than 65 with the highest rate between ages 75-84.[1] The overall survival in the elderly is significantly worse with a median of 6 months.[2] Despite this poor overall survival rate, the majority of elderly patients are still treated with the "Stupp regimen", a 6 week course of concurrent radiation therapy with temozolomide (TMZ) followed by adjuvant temozolomide.[3]

Due to limited survival, there has been interest in developing shorter courses of radiation therapy which are more convenient for the patient and families. Three prospective randomized studies have examined this question in the elderly population. Roa et al. prospectively compared standard radiation therapy (RT) with an abbreviated course of RT in patients >60 years in a phase III trial. One hundred patients with GBM were randomly assigned after surgery to receive either standard RT (60 Gy in 30 fractions over 6 weeks) or a shorter course of RT (40 Gy in 15 fractions over 3 weeks). The primary end point was overall survival. Health related quality of life (HRQoL) was assessed using the Karnofsky performance status (KPS) and Functional Assessment of Cancer Therapy-Brain (FACT-Br). No difference in overall survival or HRQoL was noted with a median overall survival of 5.1-5.6 months.[4] The International Atomic Energy Agency randomized elderly and/or frail patients to 40 Gy/15 fractions or 25 Gy/5 fractions. The median overall survival was not statistically different between the groups, 7.9 months in 25 Gy/1 week and 6.4 months in 40 Gy/3 weeks cohorts, respectively ($p = 0.988$). Median progression-free survival time was 4.2 months in both treatment arms ($p = 0.716$). With a median follow-up of 6.3 months, the quality of life between both arms at 4 weeks after treatment and 8 weeks after treatment was not different.[5] Perry et al.[6] reported a phase III randomized trial of 40 Gy in 15 treatments with or without temozolomide for patients >65. Overall survival was improved with the addition of temozolomide 9.3 mos. vs. 7.6 months. ($p<0.0001$). Quality of life showed no differences in functional domains per EORTC QLQC30 and BN20 between the two treatment arms. Therefore, from these trials, it appears that hypofractionated radiation therapy with temozolomide may be a preferable approach in the elderly given the poor overall survival.

1.1 Hypofractionated Radiation Regimens using IMRT

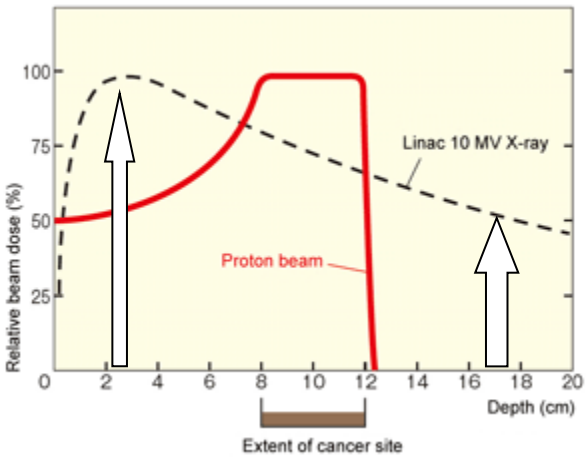
With intensity modulated radiation therapy (IMRT), this photon based technology allows for “dose painting” or the ability to preferentially deliver higher doses of radiation to MRI contrast enhanced (MRI CE) regions and lower doses to less suspicious areas at the same time. There have been a few studies that have looked into this treatment option. Omuro et al.[7] reported a phase II trial of hypofractionated IMRT delivering 36 Gy to the MRI CE tumor and 24 Gy to the FLAIR hyperintensity over 6 treatments with temozolomide and bevacizumab. With a median age of 55 years, median OS compared favorably to historical controls at 19.3 months. Quality of life was stable over time. Ney et al.[8] reported a phase II trial of hypofractionated IMRT delivering 60 Gy to the MRI CE tumor and 30 Gy to the flair hyperintensity over 10 treatments with temozolomide and bevacizumab. It was noted that treatment volumes were sizable with median volume of MRI CE tumor and FLAIR changes with margin of 131 cm3 and 342.6 cm3 respectfully. Median OS of 16.3 months was favorable to historical controls. However, they did observe significant symptomatic radiation necrosis of 50%. Iuchi et al.[9] reported a Japanese phase II trial of hypofractionated IMRT with concurrent and adjuvant temozolomide delivering 68 Gy to the MRI CE tumor and 32 Gy to the FLAIR hyperintensity over 8 treatments. The majority of progression occurred outside of the radiation field. Median survival was 20 months. However, 20/46 patients developed radiation necrosis.

Thus, these shorter fractionation regimens do provide similar overall survival compared to historical controls with higher incidence of symptomatic radiation necrosis. Proton beam therapy has the potential

to provide an improved method of balancing maximizing tumor control with greater sparing of normal tissue, possibly leading to a lower incidence of symptomatic radiation necrosis.

1.2 Use of proton beam therapy for glioma

Proton beam therapy delivers a radiation dose with positively charged atomic particles (protons), while conventional external beam RT does with photons. Unlike photons, protons have a physical property to deposit most of their energy only when they reach their target. This allows protons to deliver a radiation dose to a target more preferentially, while minimizing radiation exposure to the healthy brain, brainstem and other normal tissues. There have been several studies that have performed comparative planning to study these differences. Adeberg et al.[10] compared intensity-modulated proton therapy, volumetric-modulated arc photon therapy, and 3D conformal photon radiotherapy in anaplastic astrocytoma and glioblastoma. They found essential dose reduction to normal tissues while maintaining equal target volume coverage using proton beam therapy, particularly in reducing dose to contralaterally located critical neuronal structures, areas of neurogenesis, and structures of neurocognitive functions. Munck Af Rosenshold et al[11] compared (IMRT), inversely optimized arc therapy and spot-scanned intensity modulated proton therapy (IMPT) for high grade glioma. The IMPT technique produced the most conformal plans. In addition, IMPT offered the largest sparing of the brain and fiber tracts. Aside from normal tissue sparing, proton beam therapy has a higher relative biologic effect (RBE) as compared to conventional x-rays with a higher linear energy transfer (LET). Hirota et al.[12] demonstrated in vitro that high-LET proton particles caused greater DNA double strand breaks in glioma stem-like cells as compared to gamma rays. For all these reasons, the use of proton beam therapy may provide an improvement in local control with significantly more normal brain/structure sparing, possibly reducing the risk for symptomatic radiation necrosis.



Arrows demonstrate excess normal tissue radiation exposure

Sample plans: IMRT (photons) vs. Protons

IMRT (photons) Protons

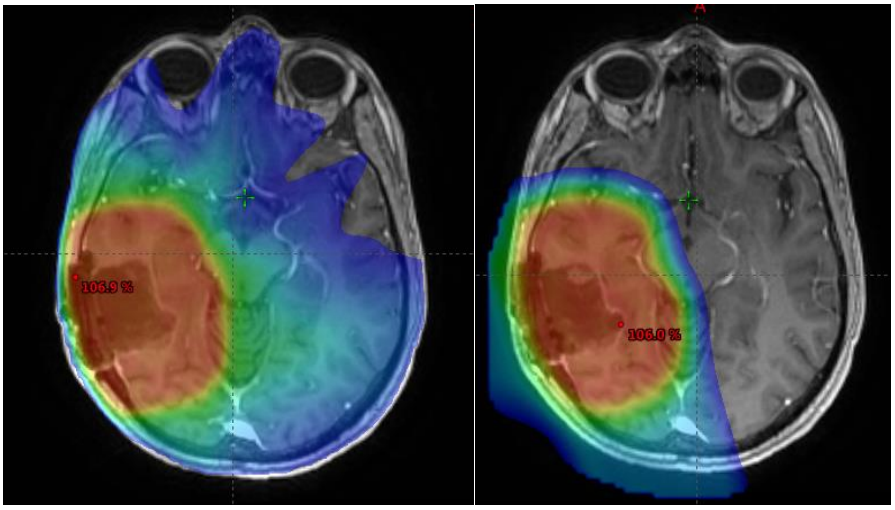


Figure 1. Illustration of differences in low-dose radiation between IMRT and protons.

1.3 Conventional imaging is inadequate to differentiate high 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, 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. Contrast enhancement 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.[13] 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 nontumoral vasogenic edema and non-uniform tumor infiltration[14,15]. 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[14]. Furthermore, tumor infiltration has been found to extend beyond areas that demonstrate abnormal T2/FLAIR or enhancement[15]. There is a critical need to incorporate imaging-based techniques to guide therapy that address these deficiencies of MRI imaging. Molecular imaging techniques provide visual information about biological processes and have the potential to improve the accuracy of RT tumor delineation, which impact the overall course of treatment and prognosis for brain tumor patients.

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

Various PET tracers have been studied for gliomas including ^{18}F-flurodeoxyglucose (18-FDG), ^{18}F-fluorodopa (^{18}F-DOPA), and 11C-methionine (^{11}C-MET). ^{18}F-DOPA transport is independent of the blood-brain barrier breakdown, allowing uptake to occur in both enhancing and nonenhancing

tumor with MRI CE . Limited studies evaluating the sensitivity of ^{18}F-DOPA indicated that although FDG PET demonstrated a higher absolute standard uptake value (SUV) compared with ^{18}F-DOPA, the sensitivity for detection of low- or high-grade tumors was 96% for ^{18}F-DOPA versus 61% for ^{18}F-FDG[16,17]. The most studied amino acid tracer is ^{11}C-MET.[18] Discrepancies of high ^{11}C-MET PET uptake extending up to 4.5 cm beyond the CE region on MRI imaging for glioma patients have been reported[19], with high MET uptake also reported extending beyond the abnormal T2 signal area[19]. Several studies have indicated ^{11}C- MET altered resection planning for a majority of both low- and high-grade gliomas[20,21]. A comparison of the performance of ^{18}F-DOPA with ^{11}C-MET concluded that ^{18}F-DOPA provided equivalent visual and quantitative SUV information when imaging cerebral lesions[22]. The short physical half-life of ^{11}C-MET limits the ability to image patients at a facility without a cyclotron. Therefore, labeling an amino acid tracer with ^{18}F-DOPA would increase the physical half-life and increase the feasibility of multi-institutional use. Unfortunately, labeling methionine with ^{18}F-DOPA 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 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.

1.5 18F-DOPA correlation with pathologic tissue

^{18}F-DOPA-PET has been in production at Mayo Clinic Rochester since 2001, used to image Parkinson's patients to study the ^{18}F-DOPA uptake in the caudate nucleus and putamen. Due to the imaging potential of ^{18}F-DOPA-PET for gliomas, an initial study by Pafundi et al.[23] correlated ^{18}F-DOPA-PET against conventional MRI for neurosurgical biopsy targeting, resection planning and radiotherapy target volume delineation. Pathologic review confirmed glioma in 22 of 23 biopsy specimens. Thirteen of 16 high-grade biopsy specimens were obtained from regions of elevated ^{18}F-DOPA uptake, while T1-CE was present in only 6 of those 16 samples. Optimal ^{18}F-DOPA-PET thresholds corresponding to high-grade disease based on histopathology were calculated as Tumor uptake/Normal tissue uptake (T/N) > 2.0. In every patient, ^{18}F-DOPA uptake regions with T/N > 2.0 extended beyond T1-CE up to a maximum of 3.5 cm. SUV was found to correlate with grade and cellularity.

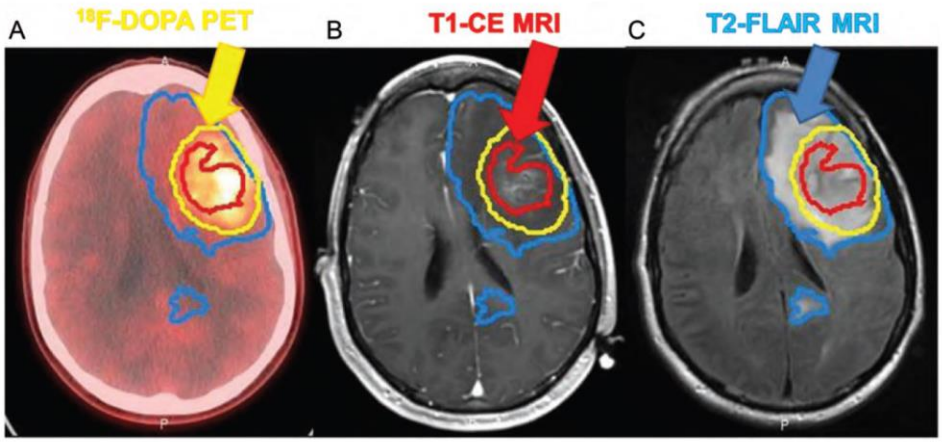


Fig. 5. Registered ^{18}F-DOPA PET-CT (A), T1-CE MRI (B), and T2-FLAIR MRI (C) contours drawn by the neuroradiologist and the ^{18}F-DOPA representing the region of high-grade disease components defined by T/N > 2.0.

Pafundi et al. Neuro Oncol 2013 Aug: 15(8), 1058-1067[23]

1.6 Preliminary data incorporating 18F-DOPA for radiation treatment planning

MC1374 is a currently active study incorporating ^{18}F-DOPA-PET to delineate areas of disease within the "boost" volume for radiation dose escalation in patients with high grade glioma. Thus far, it has been observed that 36% of patients have >30% high-density disease outside CE-MRI. From chemoradiation, dose escalating ^{18}F-DOPA areas of T/N >2.0 to 76 Gy, a change in patterns of failure has been noted with fewer in field failures. The findings were more pronounced in patients who were MGMT methylated than in patients who were unmethylated. (Unpublished, update provided by Dr. Laack)

1.7 Advanced MRI techniques

Advanced techniques using perfusion MRI(pMRI) and diffusion tensor imaging (DTI) also show promise for better differentiation of high density tumor and post-treatment radiation effect from true tumor progression compared to CE-MRI. No reported studies have performed a head-to-head comparison of ^{18}F-DOPA-PET with pMRI and DTI. Dr. L. Hu 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[24]. 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. MC1374 suggests that biopsy-validated ^{18}F-DOPA-PET thresholds may reliably delineate areas of high-grade glioma not otherwise recognized with standard MRI. MC1374 suggest that ^{18}F-DOPA-PET may more accurately identify regions of higher grade disease in patients with glioma 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.

2.0 Goals

2.1 Primary

2.1.1 Compare overall survival at 12 months for Grade IV glioma patients after radiation therapy targeting volumes designed with both ^{18}F-DOPA-PET and conventional MR image (or PET/CT) information with historical controls.

2.2 Secondary

2.2.1 Compare progression free survival at 12 months after radiation therapy targeting volumes designed with both ^{18}F-DOPA-PET and conventional MR image information with historical controls.

2.2.2 Determine acute and late effect toxicity after hypofractionated proton beam radiotherapy treatment including areas of high ^{18}F-DOPA-PET uptake (T/N>2.0)

2.3 Correlative Research

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

2.3.2 Compare differences in RT volumes identified using biopsy-validated thresholds as highly aggressive disease comparing 18F-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.

2.3.3 Evaluate quality of life after radiotherapy using EORTC questionnaires compared with historical controls from Keim-Guibert et al.[27]

2.3.4 Compare differences in proton radiation planning utilizing radiobiologic modeling/evaluation techniques performed at Mayo Clinic Rochester to Linear Energy Transfer distribution evaluation at Mayo Clinic Arizona

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.1.1 Age ≥65 years.

3.1.2 Histologically confirmed newly diagnosed Grade IV malignant glioma.

3.1.3 Planned radiation treatments at Mayo Clinic Arizona or Mayo Clinic Rochester

3.1.4 Willing to sign release of information for any radiation and/or follow-up records.

3.1.5 Provide informed written consent.

3.1.6 Patients with eGFR ≥ 60 mg/min/1.72m2

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

3.1.8 ECOG performance status 0, 1, 2

3.2 Exclusion Criteria

3.2.1 Patients diagnosed with Grades I-III glioma

3.2.2 Currently on Avastin at time of treatment

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

3.2.4 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.

3.2.5 Pregnant women, nursing women, or men or women of childbearing potential who are unwilling to employ adequate contraception.

NOTE: All women enrolled in this study will be age 65 or over, and at the determination of the PI, will not be of childbearing potential. If the radiology department requires a pregnancy test before administering the 18FDOPA injection, they may perform one per their standard of care.

4.0 Test Schedule

Tests and procedures	Pre-Treatment	Treatment Phase and Active Monitoring			Observation/ Follow-up
	≤21 days prior to registration	**Prior to RT**	**Cycle 1 RT and Chemo**	**Cycle 2-7 Chemo[7]**	**At every clinically indicated follow-up[1]**
Physical exam, wt, ECOG PS	X			X	X
Neuro history and exam	X			X	X
CBC with differential	X			X	X
^{18}F-DOPA adverse event assessment[2]		X			
^{18}F-DOPA PET/MRI[8]		X			
Assessment of Concurrent steroids and anticonvulsants		X[6]		X	X
CT simulation[3]		X			
Toxicity assessment[4]	X		X	X	X
EORTC QLQ-C30[5]		X		X	X
EORTC QLQ-BN20[5]		X		X	X
MMSE[5]		X		X	X
Advanced MRI [9]		X		X	X
Proton Beam RT			X		
Temozolomide			X	X	

1. The timing of follow-up visits for each patient will be per the clinician's discretion from the end of Cycle 7 until death or 2 years post-RT.
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. CT simulation can be done prior to or after registration, but before RT start.
4. Baseline and cycle 1 toxicities to be assessed by Radiation Oncologist, cycles 2-7 to be assessed by Neuro-oncologist. Toxicity assessment completion window during RT and chemotherapy is +/- 1 week.
5. May be done any time before registration, but must be completed prior to start of RT. Patients will complete a maximum of 6 post-baseline QOL/MMSE evaluations
6. Must be completed prior to first ^{18}F-DOPA injection.
7. Post-RT scans during Cycles 2-7 must be completed every 2 months (+/-2 weeks). All other tests and procedures in Cycles 2-7 will be completed when the patient is seen at the clinician's discretion.
8. ^{18}F-DOPA PET/CT + diagnostic MRI is an acceptable alternative to ^{18}F-DOPA PET/MRI
9. Advanced MRI is performed per standard clinical care in Arizona. Rochester will perform either MRI or advanced MRI at the physician's discretion.

5.0 Stratification Factors: None

6.0 Registration Procedures

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

6.2 Treatment on this protocol must commence at Mayo Clinic Arizona or Mayo Clinic Rochester under the supervision of a radiation oncologist.

6.3 Radiation oncologist has seen the patient and confirms the patient is a suitable candidate for this study.

6.4 Patient questionnaires are available on site.

7.0 Protocol Treatment

7.1 Radiation Therapy

Doses throughout will be prescribed in Gy(RBE)/Gy or Gy. One Gy will be the equivalent of one Gy (RBE)/Gy for proton therapy for the purposes of the descriptions below. Radiation therapy must begin within 8 weeks of the biopsy or surgical resection. The dose and fractionation will be dependent on the combined volume of the CTV of the PET(T/N>2.0) and MRI (T1 cavity+T1 contrast enhancement)-see section 7.1.9. Radiation will be delivered one fraction/day on consecutive days excluding weekends.

7.1.1 Immobilization and CT simulation: performed based on the standard of each institution.

7.1.2 Treatment planning utilizing image fusion with ^{18}F-Dopa-PET and MRI imaging. Currently, ^{18}F-DOPA is an investigational diagnostic PET radiopharmaceutical. Investigational new drug (IND) application of ^{18}F-DOPA will be submitted to FDA by Nuclear Medicine of Department of Radiology. The on-site cyclotron facilities will be able to produce ^{18}F-DOPA PET tracer for this clinical research project.

7.1.21 Timing of PET scanning

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

7.1.22 Patient preparation for PET scan

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

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

7.1.3 Simultaneous PET/MRI is preferred for this protocol. PET/CT + diagnostic MRI is also acceptable.

7.1.4 PET/CT

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

7.1.5 PET/MRI

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

7.1.52 A total of 5.0 + 10% mCi of ^{18}F-DOPA will be intravenously injected. A scout image will be acquired in order to prescribe the scan range for the image acquisition. MR images will be obtained and used for attenuation correction of the PET data and, at 10 minutes after injection of ^{18}F-DOPA, a 20 minute 3D PET acquisition will be acquired. The PET data will also be acquired concurrently in list mode; this data will be used to salvage a scan should the patient move. The PET sinograms will be reconstructed with a time-of-flight algorithm into a 300 mm field of view with a pixel size of 1.17mm and slice thickness of 2.78mm. All images will be transferred to a Radiation Oncology workstation, MIM workstation, and PACS system. Areas of high metabolic activity (defined as T/N ratio of 2.0 or greater) will be defined by Brinkman, Pafundi (MCR) or Yang (MCA).

7.1.6 Diagnostic MRI

The following MRI sequences should be obtained if possible: Sagittal T1 FLAIR, Axial DWI, Axial T2 FLAIR, Axial BRAVO ARC, Gad Axial T2, Gad Sagittal Cube T1. Advanced MRI protocols including perfusion MRI (pMRI) and diffusion tensor imaging (DTI) will be applied to this study. The estimated additional time of these two advanced MRI protocols will be approximately 10 minutes total. The pMRI DSC acquisition will be acquired as per standard perfusion DSC clinical protocol of the Radiology Department at Mayo Clinic. A dose of Gd-based contrast agent gadobutrol (Gadavist) (0.10 mmol/kg) administered before, and then another dose administered during the perfusion scan for each MRI exam is the current standard of care for the Radiology Department at Mayo Clinic. The DSC acquisition time is approximately 3 minutes. DTI data will be acquired as per standard DTI clinical protocol of the Radiology Department at Mayo Clinic. Mayo Clinic Rochester will perform advanced MRI at the physician's discretion.

7.1.62 The first post-RT MRI scan should be acquired 3-6 weeks after completing radiation treatments, to correspond with the first follow-up

appointment. Follow-up MRI scans will also be acquired at each clinically indicated appointment per the standard of care follow-up regimen.

7.1.9 Contouring and Target Definition (please refer to diagram below)

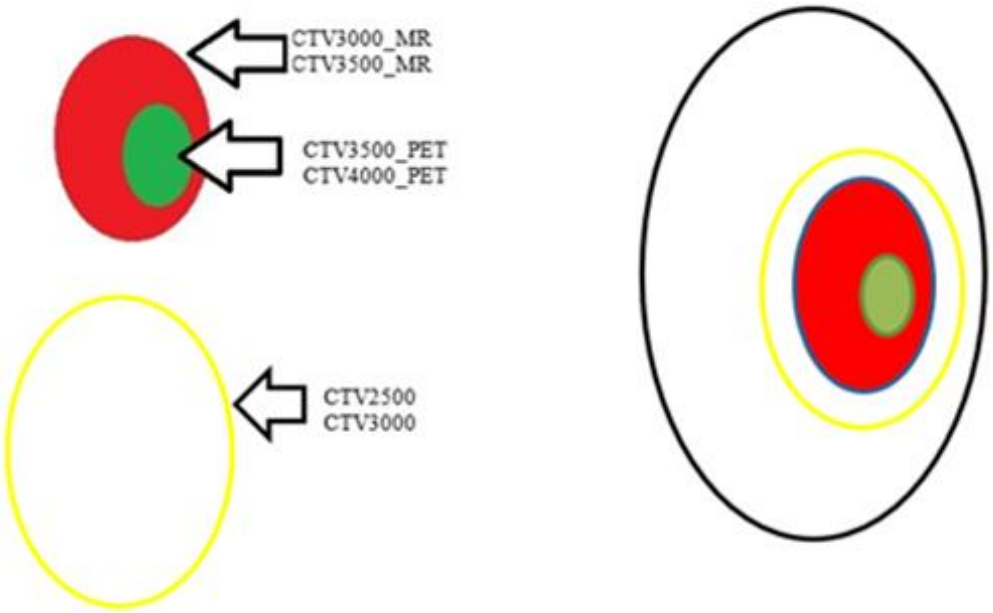
1. Co-registration with CT scans, MRI scans, and PET scans will be used in identifying the CTV volumes

2. The doses prescribed will be based on the boolean(combined) volume of CTV defined by the PET(T/N≥2.0) and the MRI areas of contrast enhancement including the surgical cavity.

    a. For patients with a combined volume ≤ 65 cc, over five treatment days, patients will receive 35 Gy to CTV3500_PET, 30 Gy to CTV3000_MR and 25 Gy(CTV2500) to boolean(combined) volume of CTV3500_PET+CTV3000_MR+**1cm.**
    b. For patients with a combined volume > 65 cc, over ten treatment days, patients will receive 40 Gy to CTV4000_PET, 35 Gy to CTV3500_MR and 30 Gy(CTV3000) to boolean(combined) volume of CTV4000_PET+CTV3500_MR+**1cm.**

3. The optimization target volume (OTV) is defined as a margin of 2 mm isotropic expansion of the CTV and edited clinically based on patterns of tumor spreading and anatomic boundaries such as skulls and nasal cavity.

4. All normal structures will be contoured on the standard of each institution.



Five Fraction Regimen (≤65cc)	**Ten Fraction Regimen (>65cc)**
CTV3500_PET=PET T/N≥2.0 CTV3000_MR=Boolean (T1_Gad+T1_Cavity) Boolean CTV3500_PET+CTV3000_MR ≤**65cc** CTV2500=(Boolean CTV3500_PET+CTV3000_MR)+1cm Optimization Target Volume (OTV)=2 mm +CTV2500	CTV4000_PET=PET T/N >2.0 CTV3500_MR=Boolean (T1_Gad+T1_Cavity) Boolean CTV4000_PET+CTV3500_MR >**65cc** CTV3000=(Boolean CTV3500_PET+CTV3000_MR)+1cm Optimization Target Volume (OTV)=2 mm +CTV3000
	*Need to make sure all CTVs are inside the brain tissue contour *Need to evaluate inclusion or exclusion of small CTV volumes at a considerable distance from bulk CTV volumes

7.1.10 Image Guidance

The Hitachi Patient Image Alignment System (PIAS) (2D) and/or CT on rails (3D) will be used for image guidance. Both are allowed under this protocol.

7.1.11 Treatment Planning

i. The prescription isodose line definition is up to the treating physician. However, we recommend that in the worst-case scenario the CTV D95% is at least 95% of the prescription dose.

ii. The optimization method can be either multi-field optimization (MFO) or single-field optimization (SFO) also known as single-field uniform dose (SFUD). SFO optimizes the spots of each proton field individually and creates a more uniform dose distribution from each beam than MFO. MFO is usually referred to as intensity-modulated proton therapy (IMPT). In MFO, spots from all the proton fields are optimized together. The inhomogeneous dose from each field is summed up to create homogeneous target coverage.

iii. Beam angles will be selected to spare normal tissues and improve plan robustness.

iv. If possible patients will be planned using SFO technique. If SFO cannot meet the dose volume constraints and plan robustness requirement, robustly optimized MFO will be used.

v. Robustness quantification to evaluate the impact of patient setup and proton beam range uncertainties will be performed. The inter-fractional setup uncertainty is assumed to be a minimum of 2 mm and proton beam range uncertainty is assumed to be a minimum of 2%. For all patients, the plan robustness will be reviewed by a physicist co-chair. We recommend that in the worst-case scenario the CTV D95% is at least 95% of the prescription dose

vi. Linear energy transfer (LET) distribution, which is calculated by an in-house developed system, will be reviewed by a physics co-chair to make sure that no high LET spots exist in the critical organs like optic chiasm and brainstem. Otherwise a new plan would be generated at the discretion of the physicist. Alternatively biologic dose distributions may be evaluated based on the RBE model developed at Mayo Clinic in Rochester and critical organs may be protected from excessive biologic dose. A new plan may be generated at the discretion of the physicist.

vii. Calculated dose distributions will be verified by comparison to a Monte Carlo/semi-analytic calculation. In cases where the CTV mean dose differs by more than 3% a new plan would be generated at the discretion of the physician.

viii. The radiobiological effects evaluation is performed based on the standard of each institution. Linear energy transfer (LET) distribution and/or biologic dose will be reviewed by the clinical team (radiation oncologist, dosimetrist, and physicist). Plans may be modified, within the protocol-specified dose-constraints, as per standard clinical practice to minimize high LET spots and/or biologically enhanced dose in the critical organs like optic chiasm and brainstem.

7.1.12 Treatment Delivery

The corresponding treatment delivery techniques as employed in the treatment planning will be used to deliver the plan.

Prescription Deviations and Goals

	Goal	Min deviation (2)	Major deviation (1)
CTV	D95% = 95%	D95% = 85% - 120%	<85% or >120%

- Prescription Dose: we recommend that in the worst-case scenario the CTV D95% is at least 95% of the prescription dose and the CTV D5% is at most 120% of the prescription dose.
- Minor deviation: CTV D95%: 85-95% of the prescription dose, CTV D5%: 110-120% of the prescription dose in the worst-case scenario.
- Major deviation: CTV 95% : <85% of the prescription dose, CTV D5%: >120% of the prescription dose in the worst-case scenario.
- Volume: The CTV must be specified on any plans with dose –volume histograms for these and all critical organs
- Critical structures in Table 7.1 with the dose volume indices up to 110% of the limit will be considered a minor deviation. Critical structures in Table 7.1 with the dose volume indices more than 120% of the limit will be considered a major deviation.

7.1.13 Critical Structures

Table 7.1 Dose volume constraints for critical structures in the nominal scenario. Minor deviation (110% of the limit) is allowed in the worst-case scenario

FIVE FRACTION	Volume	Volume Max Gy[RBE]	Max Point Dose Gy[RBE]
Optic Pathway	<0.2 cc	23 Gy[RBE]	25 Gy[RBE]
Brainstem	<0.5 cc	23 Gy[RBE]	31 Gy[RBE]
Skin	<10 cc	36.5 Gy[RBE]	38 Gy[RBE]

TEN FRACTION	Volume	Volume Max	Max Point Dose
Optic Pathway	<0.5cc	32 Gy[RBE]	37.5 Gy[RBE]
Brainstem	<0.5 cc	33 Gy[RBE]	40 Gy[RBE]
Skin	<10 cc	43.2 Gy[RBE]	45.6 Gy[RBE]

7.1.14 Quality Assurance Documentation

All plans will be reviewed by the PI and/or the co-PIs and rated as within guidelines (no deviations), minor deviation (any number of minor deviations mentioned above), or major deviation (1 or more major deviations present)

7.2 Patient Outcomes Quality of Life Assessment [Database]

7.2.1 The EORTC QLQ-C30 and QLQ-BN20 will be completed, and a MMSE will be performed per the scheduled test timepoints.

7.3 Adjuvant therapy

Patients will receive concurrent chemotherapy, temozolomide (75 mg/m2 daily, d1-7 (5 day RT regimen) or d1-14(10 day RT regimen) during radiation followed by 6 cycles of temozolomide (150-200 mg/m2) starting one month post radiation (d1-5 cycle q 28 days). This will be given and administered in standard doses as per institutional and standard regimen guidelines. Dose modifications will be done as per standard institutional guidelines. Alternating electric field therapy will be allowed during the adjuvant temozolomide phase of treatment.

7.4 Follow-up protocol

Post-treatment tumor recurrence will be monitored through follow-up imaging, using standard of care MRI (including pMRI and DTI sequences) per protocol and then when recommended by treating physician during the event monitoring phase to assess tumor response based on the Response Assessment in Neuro-Oncology (RANO) Working Group criteria until progression of disease (up to 5 years)[25]. Central review will be required to verify progression (Dr. L. Hu, neuroradiology to review).

7.5 Patterns of Failure

For those who recur, follow-up imaging at progression will be co-registered with pre-treatment imaging in the Eclipse treatment planning software (Varian Medical Systems, Palo Alto, CA) , and patterns of failure will be analyzed by determining the portion of the recurrence volume (RecVol) that falls within the delivered RT plan and classifying each recurrence as either 'central' (>95% isodose line(IDL), 'in field' (80 - 95% IDL), 'marginal' (20 - <80% IDL), or 'distant' (<20% IDL).

7.6 Outcomes

Outcomes for patients treated prospectively with the addition of ^{18}F-DOPA-PET will be determined and compared against historical controls from patients treated on NCCTG clinical trials.

7.7 Quality of life – patient reported outcomes

QOLs will be compared to high-grade glioma patients treated on Keime-Guibert et al.[27] that examined a similar group. QOL and cognitive function will be evaluated with the EORTC QLQ-C30 and QLQ-BN20 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) Monitoring and Reporting

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/protocolDevelopment/electronic_applications/ctc.htm)

a. Identify the grade and severity of the event using the CTCAE version 4.0.

b. Determine whether the event is expected or unexpected (see Section 10.2).

c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).

e. Determine if other reporting is required (see Section 10.5).

f. Note: 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).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events are those described within the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.
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 or specificity, expedited reporting is required.

NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.*

10.3 Attribution to agent(s) or procedure

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.

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 hypofractionated proton beam therapy.
Probable - The adverse event *is likely related* to hypofractionated proton beam therapy.
Possible - The adverse event *may be related* to hypofractionated proton beam therapy.
Unlikely - The adverse event *is doubtfully related* to hypofractionated proton beam therapy.
Unrelated - The adverse event *is clearly NOT related* to hypofractionated proton beam therapy.

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.

10.3.1 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.*

10.3.2 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.

10.3.3 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

10.4.1 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	

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.

Effective Date: May 5, 2011

NOTE: Refer to Section 10.3.3 for exceptions to Expedited Reporting

10.4.2 Special situations to 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 and PET tracer injection are the only procedures unique to this study. The use of hypofractionated radiation therapy is an acceptable form of treatment per National Comprehensive Cancer Network (NCCN) guidelines. 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

10.4.3 General reporting instructions

The Mayo IND Coordinator will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Use Mayo Expedited Event Report form [redacted] for investigational agents or commercial/investigational agents on the same arm.

10.4.4 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.5.1 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).

10.5.2 Death

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

10.5.3 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.

10.5.4 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 unless otherwise specified.

10.6 Required Routine Reporting

10.6.1 Baseline and Adverse Events Evaluations

CTCAE System/Organ/Class (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	
Skin and subcutaneous tissue disorders	Alopecia	x		x
Investigations	Lymphocyte count decreased	x		x
Investigations	Platelet count decreased	x		x
Investigations	Weight loss	x		x
Metabolism	Anorexia	x		x

CTCAE System/Organ/Class (SOC)	Adverse event/Symptoms	Baseline	Post Injection assessment[1]	Active Monitoring
Nervous system disorders	Enephalopathy	x		x
Nervous system disorders	Headache	x		x
Nervous system disorders	Seizure	x		x
Psychiatric disorders	Confusion	x		x

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

10.6.2 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.

10.6.2.1 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.
10.6.2.2 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.
10.6.2.3 Grade 5 AEs (Deaths) (See Section 10.5.2)

10.6.3 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.

11.0 Treatment Evaluation/Measurement of Effect

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 [25]. 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.

11.2.1 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).

11.2.2 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.

11.2.3 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.

11.2.4 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. Any evidence of progression will be also reviewed centrally by Dr. Leland Hu.

11.4 Response Criteria

11.4.1 Evaluation of Target Lesions

11.4.1.1 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.

11.4.1.2 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.

11.4.1.3 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

11.4.1.4 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

11.4.1.5 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).

	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[25] 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 [redacted] by RANO criteria
   - Clinical progression as determined by treating Oncologist
   - Cannot be considered Pseudoprogression
3. Patients with possible PsP should initially be given the Objective Status of Preliminary Progression. Once PsP or Progression is confirmed, the Objective Status can be changed accordingly.

11.4.1.6 Confirmatory Measurement/Duration of Response

11.4.1.6.1 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.

11.4.1.6.2 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.

11.4.1.6.3 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 IDH1 mutant or wildtype or not available
12.3 ECOG PS (see Appendix I): 0 vs. 1 vs. 2
12.4 Neurologic deficit: Yes vs. no
12.5 History of seizures: Yes vs. no
12.6 Gross total resection vs. Subtotal resection vs. biopsy
12.7 MGMT: Methylated vs. Unmethylated vs. not available
12.8 Family history of brain tumor: Yes vs. no
If yes, check all that apply:
_____Father/Mother
_____Brother/Sister
_____Child
_____Other (list:)
12.9 Use of alternating electric therapy: yes vs. no

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 ^{18}F-DOPA-PET for radiotherapy planning, all data up until the point of confirmation of ineligibility must be submitted.
• If the patient never received pre-RT ^{18}F-DOPA-PET, on-study material must be submitted.

13.2 Those patients who will *not* receive any radiation treatment *or* who will receive radiation treatment elsewhere will move to Event Monitoring phase and be monitored for survival until 5 years after registration.

13.3 Patients who are CR, PR, REGR, or SD will continue to obtain clinically indicated MRI scans for up to 5 years from registration.

13.4 Patients remain on study until all of the following are confirmed / complete (up to 2 years or patient refusal):

- Radiological progression by central review per RANO criteria
- Clinical progression identified by the treating oncologist
- It is more than 3 months since radiation treatments have been completed, to ensure the radiological evidence is tumor progression versus treatment response
- All follow-up study imaging during the patient visit at the time the above three conditions are met is complete

13.5 Patients who develop PD will go to the event-monitoring phase.

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[26]. ^{18}F-DOPA-PET is currently in production at these institutions, 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 protocol will assess the overall survival of newly diagnosed elderly glioblastoma patients using a one-stage phase II study design.

16.1.1 Primary endpoint: The primary endpoint of this trial is the proportion of patients alive (overall survival) at 12 months based on our hypothesis that the combination of more accurate delineation of high density tumor by ^{18}F-DOPA-PET combined with hypofractionated proton therapy will improve overall tumor control. All patients meeting eligibility criteria who have signed a consent form and who have begun treatment will be evaluable for the endpoint.

16.2 Statistical Design

A patients will be considered a success if they are alive at 12 months. Previous studies and institutional data indicate a median overall survival between 6 and 9 months, therefore we estimate median overall survival (OS) to be 7.5 months[2,4,5], which corresponds to 33% of patients surviving at 12 months. Therefore the largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 33%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen would be 50% (corresponding to a median OS of 12 months). The following single stage one-sided Exact test for proportions design uses 39 evaluable patients to test the null hypothesis that the proportion of successes is at most 33% with an overall significance level (alpha) of 0.1, and a power of 82% to detect a true success proportion of 50%.

16.2.1 Decision Rules

16.2.1.1 If 17 or fewer successes are observed in the first 39 evaluable patients that have been followed for at least 12 months, we will consider this regimen to be ineffective in this patient population. If 18 or more successes are observed in the first 39 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this patient population.

16.2.1.2 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 process.

16.2.2 Sample Size

The one-stage design to be utilized is fully described in Section 16.22. A minimum of 39 evaluable patients will be accrued to this phase-II study unless undue toxicity is encountered. We anticipate accruing an additional 4 patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Maximum projected accrual is therefore 43 patients.

16.2.3 Accrual Time and Study Duration
We anticipate enrolling 15-20 patients per year and thus plan to finish accrual of patients by year 2, leaving year 3 for follow-up and analysis. Therefore, the overall study duration is expected to be 36 months.

16.2.4 Power and Significance Levels
Assuming the number of successes is binomially distributed, the significance level is 0.075 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 can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is …	0.35	0.40	0.45	0.50	If the true success proportion is …
Then the probability of declaring that the regimen warrants further studies is…	0.16	0.37	0.62	0.82	Then the probability of declaring that the regimen warrants further studies is…

16.2.5 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 time the patients have become evaluable for the primary endpoint (see 16.2). 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 make available via a manuscript, abstract, or presentation format is when 39 patients have been followed for at least 12 months.

16.3.1 Primary Endpoint:

16.3.1.1 Definition: The primary endpoint of this trial is the proportion of alive (overall survival) at 12 months. Survival time is defined as the time from registration to death due to any cause. All patients meeting eligibility criteria who have signed a consent form and who have begun treatment will be evaluable for the endpoint. All eligible patients will be followed until death or a maximum of 5 years.

16.3.1.2 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Confidence intervals for the

true success proportion will be calculated utilizing Exact Binomial methodology. The distribution of survival time will be estimated using the method of Kaplan-Meier (1958).

16.3.1.3 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.

16.3.2 Definitions and Analyses of Secondary Endpoints

16.3.2.1 Progression free survival at 12 months after radiation therapy targeting volumes designed with both ^{18}F-DOPA-PET and conventional MRI information with historical controls. 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. The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Confidence intervals for the true success proportion will be calculated utilizing Exact Binomial methodology.

16.3.2.2 Progression Free Survival
The distribution of progression free survival times groups will be estimated using the method of Kaplan-Meier (1958). Time to disease progression is defined as the time from registration to the earliest date documenting disease progression. If a patient dies without documentation of disease progression, the patient will be censored on the last date the tumor was evaluated. If a patient is declared to be a major treatment violation, the patient will be censored on the date the treatment violation was declared to have occurred. In the case of a patient starting treatment and then never returning for any evaluation, the patient will be censored for progression on the last day of therapy.

16.3.2.3 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 hypofractionated proton beam therapy will be determined, with acute RT toxicities graded using Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (available at http://ctep.cancer.gov).

16.4 Correlative Research

16.4.1 Compare RT treatment volumes defined by MR only with RT treatment volumes defined with both PET and MR information. To assess the impact of integrating PET on target definition, the treating radiation oncologists will first define the treatment volumes for CTV_{MR} and using the MR images while blinded to the PET study. Then the PET study will be reviewed with the planning CT and MRI studies to allow contouring of the CTV_{PET} defined by the T/N ratio of >2.0, respectively. The contours will be combined by the treating radiation oncologist and then expanded as described above. The volume of overlap and non-overlap between the CTV 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. Alternate metrics for comparison will also be assessed, including spatial overlap, distance, correlations and 3D shape comparisons.

16.4.2 Compare differences in RT volumes identified using biopsy-validated thresholds as highly aggressive disease comparing 18F-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. Paired t-test statistical analysis will be performed to determine if any differences exist and the level of statistical significance between RT volumes based on ^{18}F-DOPA uptake and the measures mentioned above.

16.4.3 Quality of Life
Evaluate quality of life after radiotherapy treatment targeting dose escalated volumes defined to include high ^{18}F-DOPA-PET uptake. QOL surveys will be compared to data from historical controls[27]. Quality of life will be assessed at baseline and at each MRI evaluation (up to 6 evaluations). QOL will be measured using the EORTC QLQ-C30, a 30-item patient-reported questionnaire about patient ability to function, symptoms related to the cancer and its treatment, overall health and quality of life, and perceived financial impact of the cancer and its treatment. 28 of the 30 items are measured on a 1-4 scale (1=not at all; 4=very much) with the remaining two items (overall health and overall quality of life) scored on a 1-7 numeric analogue scale (1=very poor; 7=excellent). The recall period for the EORTC QLQ-C30 is one week. The EORTC QLQ-C30 is the product of more than a decade of collaborative research and to date, more than 2200 studies using the EORTC QLQ-C30 have been registered with the EORTC (Fayers et al, 2001 [EORTC Scoring Manual]). Of the 30 items, 24 aggregate into nine multi-item scales representing various HRQoL dimensions: five functioning scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, pain and nausea), and one global measure of health status. The remaining six single-item scales assess symptoms: dyspnea, appetite loss, sleep disturbance, constipation and diarrhea, and the perceived financial impact of the disease treatment. High scores indicate better QoL for the global health status and functioning scales, and worse QoL for the symptom scales. The QLQ-BN20 contains 20 items, 13 of which aggregate into four scales assessing future uncertainty, visual disorder, motor dysfunction, and communication deficit. The remaining single items assess other disease symptoms (e.g. headaches and seizures) and treatment toxic effects (e.g. hair loss) For all these scales, a higher score represents worse QOL.

The patient-completed questionnaires will be administered to all willing patients via paper or electronic format in clinic at baseline and at each evaluation. Questionnaires will be scored according to the published scoring algorithms.

Scale score trajectories over time will be examined using stream plots and mean plots with standard deviation error bars overall. Analysis will include change from baseline using t-tests and mixed linear models to test for changes at each time point and non-zero slope respectfully.

16.4.4 Compare differences in proton radiation planning utilizing radiobiologic modeling/evaluation techniques performed at Mayo Clinic Rochester to Linear Energy Transfer (LET) distribution evaluation at Mayo Clinic Arizona. Paired t-test statistical analysis will be performed to determine if any differences exist and the level of statistical

significance between proton plan metrics based off the two modeling/evaluation techniques.

16.5 Data and Safety Monitoring Plan

16.5.1 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.

16.5.2 Adverse Event Stopping Rules:
As no reactions to ^{18}F-DOPA have been reported within Mayo Clinic Rochester, toxicity testing reported in the literature revealed no deleterious effects (section 15.0), 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 DSMB. There have been no reports in the literature of the occurrence of NSF in patients with normal renal function[28,29] . 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[28,29]. Therefore no reactions are anticipated. As such, if at any time a patient develops NSF enrollment will be suspended so that details of the episode can be examined and a trial recommendation will be formulated and presented to the MCCC DSMB.

Using the hypofractionation approach described in Section 7, previous studies have successfully used hypofractionation without significant increases in acute or late adverse effects[4,5]. However, some studies with more aggressive, higher daily doses of hypofractionation have reported increased toxicity. Nonetheless, both acute (available at http://ctep.cancer.gov) and late[30] 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 DSMB

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

16.6 Results Reporting on ClinicalTrials.gov

16.6.1 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 36 months after the study opens to accrual.

16.6.2 Definition of Primary-Endpoint Completion Date (PCD): The PCD is the date at which the last patient has been followed for 12 months.

16.7 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 and gender subsets are shown in the following table:

Accrual Targets			
	Sex/Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	1	2	3
Not Hispanic or Latino	16	24	40
Ethnic Category: Total of all subjects	17	26	43
Racial Category			
American Indian or Alaskan Native	1	0	1
Asian	0	1	1
Black or African American	1	2	3
Native Hawaiian or other Pacific Islander	0	0	0
White	15	23	38
Racial Category: Total of all subjects	17	26	43

Ethnic Categories:

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

Not Hispanic or Latino

Racial Categories:

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

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

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

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

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

17.0 Pathology Considerations/Tissue Biospecimens

N/A

18.0 Records and Data Collection Procedures

18.1 Submission Timetables

Initial Material(s)

CRF	**Pre-Treatment** (Compliance with Test Schedule Section 4.0)
Patient Eligibility	≤2 weeks after registration
Demographics	
On-Study	
Adverse Events: Baseline	
Patient Status: Baseline	
Patient Assessments	
MMSE Form	
Patient Questionnaire Booklet	
Concurrent Steroid and Anticonvulsant Treatment Form	
Off Treatment	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

Test Schedule Material(s)

CRF	**Treatment Phase and Active Monitoring** (Compliance with Test Schedule Section 4.0)			**Event Monitoring[7] / Follow-up** (Compliance with Test Schedule Section 4.0)
	≤4 weeks after each evaluation during RT	≤1 week after ^{18}F-DOPA-PET scan	End of Treatment	
Radiation Therapy	X		X	
Adverse Event Form (Post Injection of ^{18}F-DOPA)		X[4]		
Radiation Therapy Adverse Event Form (Toxicity)			X[5]	X[5]
Off Treatment[2]	X		X	X
Patient Status Form	X		X	X
Consent Withdrawal[2]	X	X	X	X

CRF	Treatment Phase and Active Monitoring (Compliance with Test Schedule Section 4.0)			Event Monitoring[7] / Follow-up (Compliance with Test Schedule Section 4.0)
	≤4 weeks after each evaluation during RT	≤1 week after ^{18}F-DOPA-PET scan	End of Treatment	
Lost to Follow-up[2]	X		X	X
Patient Questionnaire Booklet[3]			X[6]	X[6]
Concurrent Steroid and Anticonvulsant Treatment Form			X	X
MMSE			X[6]	X[6]
Imaging Form[8]		X		X

1. Acute toxicity will be assessed during standard of care monitoring by the radiotherapy team during the course of treatment.
2. When applicable.
3. Survey will need to be entered manually if it is not completed electronically
4. Done approximately 15-20 minutes post injection of ^{18}F-DOPA after scan is completed and if AE observed a second AE assessment is required ≤24 hours post injection.
5. Late toxicity will be assessed during standard of care appointments. To be submitted ≤2 weeks after each clinically indicated MR scan.
6. Patient will complete a maximum of 6 post-RT QOL evaluations
7. Follow-up is until death or a maximum of 5 years from the time of registration.
8. See Appendix VI.

18.2 Data Handling and Record Keeping

18.2.1 Confidentiality

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

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

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

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

18.2.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. Source documents are kept in a secure location that is locked and requires approved access.

18.2.3 Case Report Forms
The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

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

The investigator will retain the specified records and reports for;
1. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" [redacted]

19.0 Study Finances

19.1 Costs charged to patient: Routine clinical care

19.2 Tests to be research funded: ^{18}F-DOPA-PET scan and costs incurred for providing copies of imaging from local MD.

19.3 Other budget concerns: None.

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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
The European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: bbbb
Your birthdate (Day, Month, Year): cececdde
Today's date (Day, Month, Year): 31 cececdde

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4

15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix III
The European Organization for Research and Treatment of Cancer (EORTC) QLQ-BN20

EORTC QLQ - BN20

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
31.	Did you feel uncertain about the future?	1	2	3	4
32.	Did you feel you had setbacks in your condition?	1	2	3	4
33.	Were you concerned about disruption of family life?	1	2	3	4
34.	Did you have headaches?	1	2	3	4
35.	Did your outlook on the future worsen?	1	2	3	4
36.	Did you have double vision?	1	2	3	4
37.	Was your vision blurred?	1	2	3	4
38.	Did you have difficulty reading because of your vision?	1	2	3	4
39.	Did you have seizures?	1	2	3	4
40.	Did you have weakness on one side of your body?	1	2	3	4
41.	Did you have trouble finding the right words to express yourself?	1	2	3	4
42.	Did you have difficulty speaking?	1	2	3	4
43.	Did you have trouble communicating your thoughts?	1	2	3	4
44.	Did you feel drowsy during the daytime?	1	2	3	4
45.	Did you have trouble with your coordination?	1	2	3	4
46.	Did hair loss bother you?	1	2	3	4
47.	Did itching of your skin bother you?	1	2	3	4

48.	Did you have weakness of both legs?	1	2	3	4
49.	Did you feel unsteady on your feet?	1	2	3	4
50.	Did you have trouble controlling your bladder?	1	2	3	4

Appendix IV
Mini Mental State Exam (MMSE)

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."

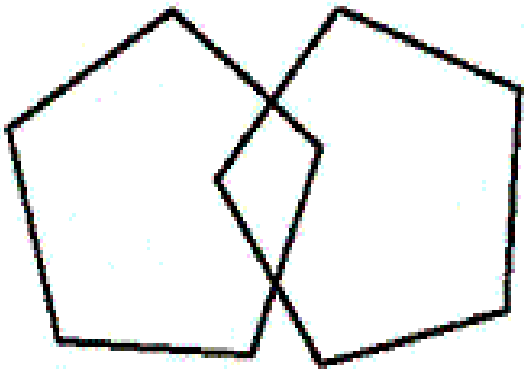
_____/1 Read and obey: "Close your eyes."

_____/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.



1) ion of brain parenchyma and n sparing for superficial targets.
2) igittal image to define axial slice for ially to include midbrain (typically ").
3)
4) 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.
5) Eyes: In Eclipse contour the globe on the CT data set and check on any MR data set. IF discordant use CT data set.
6) Hippocampus: Based on RTOG guidelines (please see NRG/RTOG contouring atlas for reference), 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.
7) Hippocampus PRV: 5mm expansion of hippocampus contour

8) 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. It is bounded laterally by the optic radiations and posteriorly by the interpeduncular fossa and posterior commissure. Continue the contours until the hypothalamus terminates antero-rostrally at the fornix and anterior commissure.
9) 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.
10) Lens: contour on CT data set (or use auto contour in GE prior to exporting to Eclipse).
11) 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. Remember the MR should only be a guide and the CT truly defines the optic chiasm. Also do not include the carotid arteries as part of the optic chiasm contour.
12) 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.
13) Optic structures PRV: 3 mm expansion of the optic nerve and chiasm contours
14) 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 clinoids and the medial edge of the sphenoid bone.
15) 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).
16) 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.
17) Skin: standard skin definition is 5mm rind on body. However, in the head, deep skin border is limited by skull. If 5mm is used, bones should be removed from skin volume. 3mm is often a closer approximation of skin in the scalp.

Appendix VI

PLACE LABEL HERE

Protocol Number: MC1774

Patient ID: _____ Patient Initials: _____ (L F M)

Institution Number: _____

Institution: _____

MAYO CLINIC CANCER CENTER

Imaging Form

ALL ITEMS MUST BE COMPLETED

Are data amended? *(check one)* ☐Yes ☐No

(If data amended, please circle in red when using paper forms)

Current Cycle Number: ___

IMAGING DETAILS

MR

Was conventional MR imaging completed? *(check one)*

1☐Yes. If Yes: Date of conventional MR imaging: *(mm/dd/yyyy)* ____/____/_____

2☐No. If No, Primary Reason conventional MR imaging not completed:

99☒Other (not per protocol), specify _____

Was perfusion MR imaging completed? *(check one)*

1☐Yes. If Yes, date perfusion MR imaging completed? *(mm/dd/yyyy)* ____/____/_____

2☐No. If No, Primary Reason perfusion MR imaging not completed:

99☒Other (not per protocol), specify _____

Was diffusion MR imaging completed? *(check one)*

1☐Yes. If Yes, date diffusion MR imaging completed? *(mm/dd/yyyy)* ____/____/_____

2☐No. If No, Primary Reason diffusion MR imaging not completed:

99☒Other (not per protocol), specify _____

PET

Weight (kg):_____ *(used for this cycle, round to the nearest tenth)*

Is this patient of childbearing potential? *(check one)* 1☐Yes 2☐No

If Yes: Negative pregnancy test date *(≤ 48 hours prior to injection of study drug)*: *(mm/dd/yyyy)* ____/____/_____

Pregnancy test date time:_____:_____*(military time)*

Was FDOPA-PET imaging completed? *(check one)*

1☐Yes. If Yes: Date of FDOPA-PET imaging: *(mm/dd/yyyy)* ____/____/_____ Time of Injection:_____:_____*[Range: 0000 (midnight) to 2359 (11:59 pm)]*

FDOPA Dose amount:_____.____mCi

Time of FDOPA-PET imaging:_____:_____*[Range: 0000 (midnight) to 2359 (11:59 pm)]*

Duration of scan *(minutes)*: _____

2☐No. If No, Primary Reason FDOPA-PET imaging not completed: *(check one)*

49☐Allergic reaction
223☐Vasovagal reaction
218☐Bruising
229☐Rashmaculo-papular
99☐ Other (not per protocol), specify_____