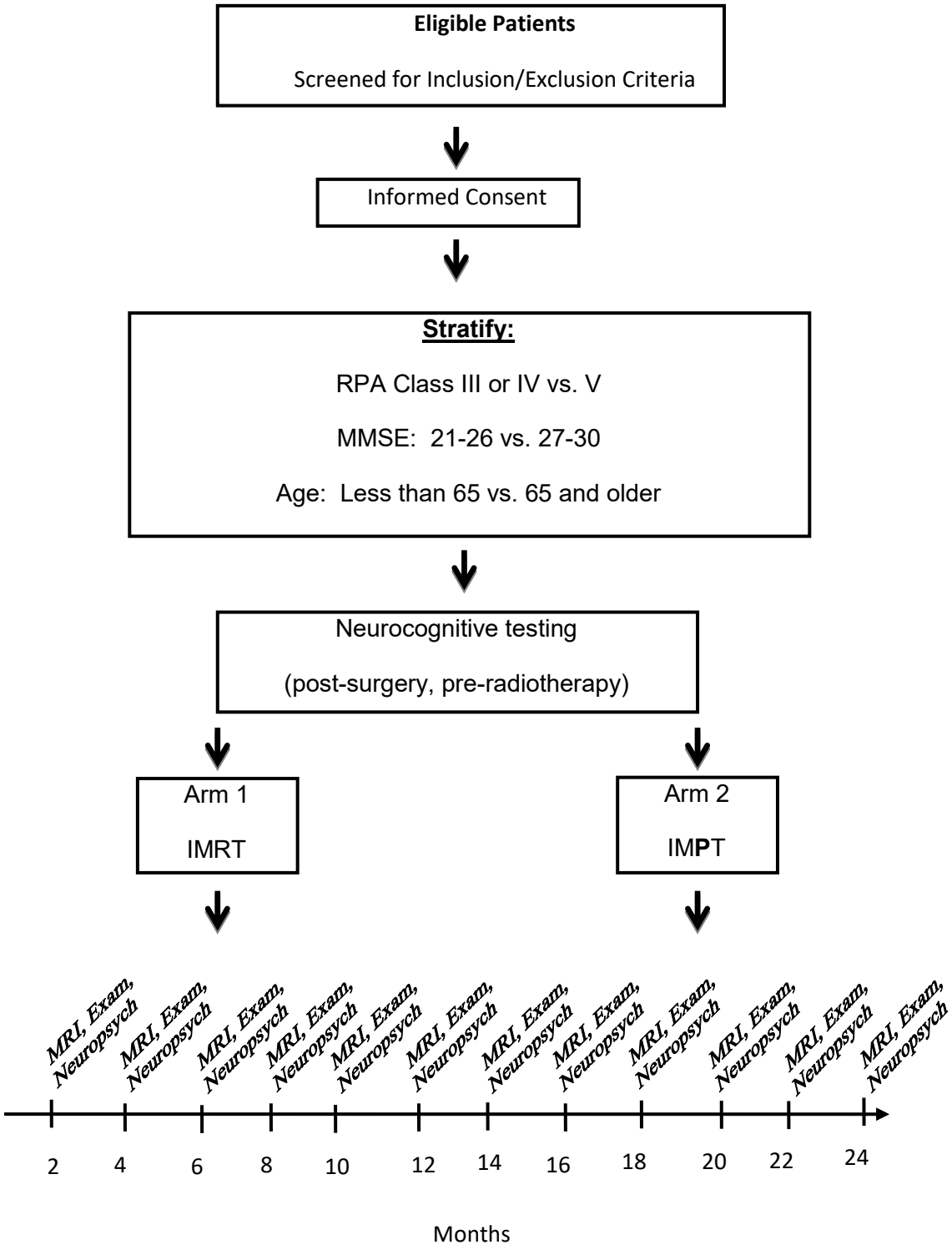
A prospective Phase II randomized trial to compare intensity modulated proton radiotherapy (IMPT) vs. intensity modulated radiotherapy (IMRT) for newly diagnosed Glioblastoma (WHO Grade IV)

1.0 Abstract

Glioblastoma (GBM) accounts for 25% of all primary central nervous system (CNS) tumors in adults and historically has been associated with median survival times of less than a year [1]. However, the addition of temozolomide to radiotherapy has resulted in significant improvements in survival, especially for certain subsets of patients [2]. With the improvement in survival times there are growing concerns about the negative effects of treatment, especially the potential for cognitive deficits after cranial radiotherapy. Decreasing the amount of brain exposed to radiation has a significant impact on cognitive function after radiation [3-5]. Proton radiotherapy is a treatment modality which has been safely and effectively used in the treatment of GBMs with low rates of toxicity such as radiation necrosis [6, 7]. Additionally, there is some pre-clinical evidence that supports greater impact on tumor cell death with protons compared to photons [8]. Previous studies have shown that intensity modulated proton therapy (IMPT) can allow for more conformal target coverage than conventional intensity modulated photon radiation therapy (IMRT) while minimizing doses to normal tissues such as the contralateral hippocampus [9]. The decreased dose to critical normal brain tissue resulting from conformal proton radiotherapy has been suggested to translate into improved cognitive function based on radiation dose cognitive effect models [10]. Additionally, improved conformality of dose delivery by IMPT may allow for dose escalation in the treatment of GBM which has been demonstrated to improve median survival time as a result of improved central control of tumors [11]. The purpose of the current study is to prospectively assess the cognitive sequelae, quality of life, and local control outcomes of patient with glioblastoma treated with IMPT versus IMRT.

2.0 Schema


Eligible Patients
Screened for Inclusion/Exclusion Criteria
Informed Consent
Stratify:
RPA Class III or IV vs. V
MMSE: 21-26 vs. 27-30
Age: Less than 65 vs. 65 and older
Neurocognitive testing
(post-surgery, pre-radiotherapy)
Arm 1
IMRT
Arm 2
IMPT
MRI, Exam, Neuropsych
2
4
6
8
10
12
14
16
18
20
22
24
Months

Eligibility Checklist

1. _____ Histological diagnosis of: Glioblastoma or Gliosarcoma (WHO Grade IV) adapted RPA class III, IV, or V (Y/N)
2. _____ Age 18 years or older at registration (Y/N)
3. _____ Informed consent must be signed (Y/N)
4. _____ Patient has a baseline Mini Mental Status Examination score of 21 or greater (Y/N)
5. _____ KPS ≥70 (Y/N)
6. _____ Eligible to have treatment by IMRT or IMPT as determined by radiation oncologist (Y/N)
7. _____ Patient is able to obtain an MRI with and without contrast with a glomerular filtration rate (eGFR) ≥ 30 mg/min/1.72m^2 (Y/N)
8. _____ Patient has adequate liver, renal, and hematologic function within 14 days of registration as defined by Aspartate Amino Transferase (AST)/Alanine Amino Transferase (ALT)/Alkaline Phosphatase < 3 times normal, creatinine ≤1.7 mg/dl, BUN ≤ 35mg/dl, absolute neutrophil count ≥1,800 cells/mm^3, Hemoglobin ≥ 10 g/dl, and platelet count > 100,000 (Y/N)
9. _____ Patient is able to adequately read, write and speak to participate in the cognitive and quality of life assessments, allowing for mild to moderate deficits in these functions due to tumor (Y/N)
10. _____ Patient is planning to receive concurrent temozolamide (Y/N)
11. _____ Patient has no prior history of brain radiation (Y/N)

12. _____ Patient has not had prior surgical resection of brain for other brain tumors (Y/N)
13. _____ Female patients of child bearing potential are not pregnant based on serum Beta-HCG test (Y/N)
14. _____ Patient does not have gliomatosis (Y/N)
15. _____ Patient has not had Glialdel (BCNU) wafers implanted (Y/N)
16. _____ Patient weight is less than or equal to 136 kilograms (Y/N)

3.0 Objectives

3.1 *Primary Objectives*

3.1.1 To assess whether treatment with IMPT results in longer time to cognitive failure compared with IMRT. Cognitive failure is defined as the first cognitive failure on any of the following six cognitive outcome variables: Hopkins Verbal Learning Test Revised (HVLT-R) Total Recall, HVLT-R Delayed Recall, HVLT-R Delayed Recognition, Controlled Oral Word Association (COWA), Trail Making Test (TMT) Part A or Part B.

3.2 *Secondary Objectives*

3.2.1 To determine local control in the brain post radiation treatment.

3.2.2 To determine overall survival in each treatment arm.

3.2.3 To assess quality of life measured at two month intervals for a total of two years post-radiotherapy for both treatment arms.

3.2.4 To assess the pattern of cognitive change in memory at two month intervals for two years post-treatment as well as executive function and processing speed.

3.2.5 MRI diffusion weighted images (DWI) and reconstructed apparent diffusion coefficient (ADC) maps will be analyzed to see if there is a difference between pre- and post-treatment scans. These will also be analyzed for differences between the two treatment modalities.

3.2.6 To evaluate if diffusion tensor imaging (DTI) correlates to the cognitive changes and if there are differences between the two treatment modalities.

3.2.7 To assess the pre-treatment factors of recursive partitioning analysis (RPA) class and mini mental status examination (MMSE) in the predictive determination of local and distant control and cognitive outcome in each treatment arm.

3.2.8 To assess the correlation between location of primary lesion, total volume of intracranial disease, and cognitive outcome in each treatment arm.

3.2.9 To determine the relationship between MGMT promoter methylation status and cognitive and local control outcomes.

3.2.10 To document and descriptively compare post-treatment adverse side effects between the two treatment arms.

3.2.11 To determine the relation between dosimetric parameters and cognitive and local control outcomes.

3.3 *Correlative objectives*

3.3.1 To determine if Apo E (i.e., Apo E2, Apo E3, and Apo E4) genotyping may prove to be a predictor of radiation induced neurocognitive decline (or neuro-protection).

3.3.2 To determine if inflammatory markers (i.e., IL-1, IL-6, and TNF-α) may prove to be predictors of radiation induced neurocognitive decline.

3.3.3 To determine if hormone and growth factors [i.e., glucocorticoids (e.g., cortisol), gonadal steroids (e.g., estradiol, testosterone, progesterone),

growth hormone, human chorionic gonadotropin (hCG), insulin-like growth factor-1 (IGF-1), and neuronal growth factor (NGF)] may prove to be a predictor of radiation induced neurocognitive decline.

3.3.4 To validate the prognostic significance of a combined multi-molecular marker survival classifier called the Molecular Clinical Prognosticator (MCP).

4.0 Background

Gliomas represent the most common primary brain tumor in the adult population. Malignant gliomas include anaplastic astryocytoma (AA) and glioblastoma multiforme (GBM) and have an annual incidence of 3 to 4 per 100,000, with over 80% of these being GBMs [12]. The standard treatment for glioblastoma is maximal safe resection followed by involved-field radiation. A pooled analysis of six randomized trials demonstrated that there is a significant survival benefit to the addition of radiation therapy after surgical resection [13]. Historically outcomes have been quite poor with median survival of less than one year for GBM [12].

Recently, combined modality treatment including the addition of concurrent and/or adjuvant temozolomide has resulted in significant improvement in outcomes for glioblastoma patients [2, 14]. Stupp et. al. demonstrated a 2 year overall survival (OS) rate of 27.2% with concomitant and adjuvant temozolomide as compared to a 10.9% 2 year OS rate with radiation alone [2]. This response was found to be durable at 5 years of follow up. Indeed, patients with favorable prognostic categories such as MGMT promoter methylation had even better survival outcomes. With improved outcomes and longer survival an increasing number of patients are at risk for secondary adverse effects from radiation treatment, particularly cognitive decline.

Cognitive function has been increasingly recognized as a key primary outcome measurement following cranial radiotherapy. Several studies have suggested that in high grade glioma patients tumor progression was the dominant cause of cognitive decline [15-17]. However, these studies were done in the era prior to the introduction of combined modality treatment when median survival was less than one year. While tumor progression is a key factor in cognitive function, prolonged survival with combined modality treatment will also lead to an increasing number of patients who develop treatment related late toxicity.

Data in low grade glioma patients suggests that the amount of brain exposed to radiation as well as the dose of radiation has a significant impact on cognitive function [3, 4, 18]. Similarly, metastatic brain cancer patients receiving stereotactic radiation have improved cognitive outcomes compared to patients treated with whole brain radiation therapy [19]. This has led to an increased interest in using more focused radiation therapy for glioblastoma.

Currently most patients with glioblastoma are treated using either 3D conformal or intensity modulated radiation therapy (IMRT) with photon beams. These modalities allow for conformal dosing to tumor while minimizing dose to surrounding normal structures. However,

surrounding normal structures continue to receive low to moderate doses of radiation. Proton beam therapy is an alternative technology which may provide more conformal dosing with less dosing to normal structures.

Proton radiotherapy has been previously demonstrated to be safe and effective in the treatment of high grade gliomas [6, 7, 20]. Additionally, there is preclinical evidence that proton radiotherapy may have a greater impact on tumor cell death. Moertel et al. have demonstrated that human glioblastoma cells in culture experience increased G2 cell cycle arrest and decreased DNA double strand break repair when irradiated with protons versus photons [8]. This suggests a potential advantage of proton therapy in glioblastoma patients.

Previous studies have also demonstrated that IMPT can allow for more conformal dosing than IMRT. IMPT can take advantage of proton characteristics such as less lateral scatter, lack of exit dose, and steep distal dose fall-off to increase conformality. For example, Rosenschold et al. compared treatment plans using IMRT versus IMPT for high grade glioma patients. They found increased planning target volume (PTV) coverage conformality with IMPT. Additionally, IMPT plans had increased sparing of healthy tissue both for whole brain doses as well as to critical structures such as the contralateral hippocampus [9].

Decreased dosage to critical normal brain tissues has been suggested to translate into improved cognitive function. Merchant et al. compared dose characteristics for four types of common childhood brain tumors treated using conformal protons versus photons and in dose-volume modeling systems found that proton plans resulted in better cognitive outcomes. Specific advantages included decreased IQ loss, less cochlea damage, and decreased endocrine effects[10]. The study of long term benefit of proton therapy in pediatric patients will require years of follow up but the preliminary results are encouraging. Similarly Arvold et al. modeled doses for protons versus photons in the treatment of benign meningiomas. They showed that protons could decrease the risk of radiation associated secondary malignancies by half and that lower doses to critical structures supporting cognitive functions such as memory including the temporal lobe and hippocampus could be achieved with proton plans [21].

While the theoretical dosimetric advantages of proton plans are intriguing we do not have randomized data comparing cognitive outcomes in glioblastoma patients treated with these two modalities. We hypothesize that IMPT will result in improved cognitive outcomes. In this trial we propose to address this question by prospectively randomizing patients with glioblastoma to treatment with IMRT versus IMPT. Patients will be stratified by RPA class, Mini Mental Status Examination score (21-26 vs. 27-30)[17], and age (less than 65 vs. 65 and older). These factors are known to have prognostic significance. The primary endpoint will be time to first cognitive failure on any of the following six cognitive test variables: HVLT-R Total Recall, HVLT-R Delayed Recall, HVLT-R Delayed Recognition, COWA, and TMT A or B. Secondary endpoints will include local control and overall survival outcomes as well as quality of life. Addressing this question in a prospective randomized fashion can be accomplished at MDACC given the high volume of cancer patients with glioblastoma treated at our center.

5.0 Background Information on Treatment Modalities and Correlative Studies

5.1 Background on Treatment Modalities

Intensity modulated radiotherapy uses photon beams to deliver treatment. The advantage of this treatment modality over traditional or 3D-conformal radiation lies in increasing dose conformality. By dividing each radiation field into a number of separate beamlets, using inverse planning and intensity modulation, and then adding beamlets together to form a cumulative dose distribution the treatment can be highly sculpted to the tumor. In multiple tumor types this technique has been shown to greatly reduce side effects while maximizing tumoricidal doses to the target. However, this technique is constrained by the physical properties of photons. Photons deposit dose as they travel through normal tissues both upon entrance and exit after passing through the target. As multiple beam angles are used, one criticism of IMRT is the "low dose bath" that surrounding normal tissues receive. While IMRT is a substantial improvement over conventional or even 3D techniques and is now the standard for irradiation of glioblastoma at our institution, IMPT may be even more advantageous.

Intensity modulated proton therapy is also a method of delivering ablative doses to the primary tumor while minimizing radiation to surrounding normal structure. The basis of the advantage of protons over photons in general lies in their action in exposed tissues. Specifically, in contrast to photons which are absorbed throughout the course of their beam path, protons have a finite range of action that is dependent on the initial proton energy. Protons traverse most of the beam path and then deposit their energy near the target in the Bragg peak with little or no exit dose. When several beams of closely spaced energies are combined a spread-out Bragg peak (SOBP) can be created which results in a modulated proton beam. In IMPT there is simultaneous optimization of all Bragg peaks from all incident beams. This ability to modify treatment voxel by voxel results in increased dose conformality. IMPT was pioneered at the Paul Scherrer Institute in Switzerland but is now being offered commercially by Varian Medical Systems (Palo Alto, CA). IMPT has been proposed as being most useful in treating complex field shapes such as brain tumors.

In short, IMRT and IMPT have many similarities. Both involve the delivery of fractionated, daily radiation to targeted brain tissues although they accomplish this with different modalities. In both treatment types radiation is highly targeted to specific sites in the brain to include gross residual disease as well as areas at high clinical risk of microscopic disease. However, as delineated above there are differences between the two treatment modalities. In particular the decreased exit and low doses to normal structures with IMPT suggest that there may be a significant difference between the two modalities in regards to cognitive outcomes. However, there is an increased cost associated with IMPT and as stewards of our healthcare system it is important to show if there is a measurable clinical benefit associated with the use of IMPT.

5.2 Background for correlative studies

5.2.1 Genetic Markers

Apolipoprotein E (ApoE) is an important factor in remodeling and repairing neurons in response to injury or stress through its lipid transport function. In fact, recent data suggests that patients having the Apo E4 isoform realize Alzheimer's dementia far earlier than those without it [22]. This allele is present in 16% of the general population and 50% of patients with late onset Alzheimer's dementia [23]. Given the similar mechanisms of dementia between Alzheimer's dementia and radiation induced dementia (e.g. vascular or metabolic), Apo E4 genotyping may prove to be a predictor of radiation induced neuronal damage. The Apo E4 protein binds rapidly and tightly to beta amyloid. Normally beta amyloid exists in a soluble form. However, when bound by Apo E4 protein, beta amyloid becomes insoluble and is more likely to be deposited in plaques which may lead to changes in microvasculature, ultimately leading to neurocognitive decline. Further, patients with just one copy of the Apo E4 allele have demonstrated accelerated hippocampal volume loss which can also compromise neurocognitive function [24]. Recent preclinical mouse data from Crawford and Villasana have shown neurogenesis in the hippocampus and hippocampal dysfunction depending on Apo E status [25, 26]. Patients with Apo E2 and Apo E3 alleles, on the contrary, tend to have one quarter the risk of developing Alzheimer's disease. It is felt that the E2 and E3 alleles are able to facilitate repair and protection from neuronal damage. Apo E genotyping will be performed to assess whether a subgroup of patients exists that is genetically predisposed to developing neurocognitive decline (or neuroprotection).

5.2.2 Inflammatory Markers

Markers of inflammation are elevated with aging and their increase has been associated with cognitive decline [27, 28]. Epidemiological and retrospective data reveals an improvement in neurocognitive function with the use of NSAIDs in patients with Alzheimer's dementia, supporting an inflammatory process involved in neurocognitive decline [23]. Chronic inflammation as a result of mass effect from tumor or treatment related inflammation may be associated with neurocognitive deficits and can be measured in plasma. Interleukin 1 (IL-1), Interleukin 6 (IL-6), and Tumor Necrosis Factor alpha are pro-inflammatory cytokines that are a measure of inflammation and have been shown to be elevated in patients with Alzheimer's dementia [29-32]. In this study, inflammatory biomarkers will be measured at baseline (after registration, but prior to treatment) and at each follow-up visit when neurocognitive testing is performed.

5.2.3 Hormone and Growth Factors

Aging and memory decline is associated with the disruption of hormone regulation, including glucocorticoids, gonadal steroids, and growth hormone [33]. Cortisol, human chorionic gonadotropin (hCG), insulin-like growth factor-1

(IGF-1), and neuronal growth factor (NGF), have all recently been associated with cognitive decline in Alzheimer's disease [34, 35]. ELISA testing of serum specimens for each hormone and growth factor will be performed at baseline (after registration, but prior to treatment) and at each follow-up visit when neurocognitive testing is performed.

5.2.4 Molecular Clinical Prognosticator (MCP)

Classification according to both molecular biomarkers and the well-validated Glioma RTOG recursive partitioning analysis (RPA) classification [36, 37] is important for accurate survival prediction. Robust survival classification are important both in planning randomized trials for stratification and for selection of patients for appropriate therapy. In order to increase the survival classification resolution while minimizing the impact on patient enrollment requirements, we have developed a new prognostic classifier, the MCP. The MCP was developed using methodologies suitable for archival, formalin-fixed, paraffin-embedded (FFPE) tissue. In its development, a generalized "training and validation" approach was used in which the statistical model was built on a set of cases to optimize survival class discrimination (training set) and a subsequent, blinded and independent cohort was used to validate this model (validation set). The training set consisted of approximately 250 GBM specimens that were then validated using 725 specimens obtained prospectively as a requirement for randomization in the RTOG 0525 trial. It is thus a fully validated prognostic classification scheme.

The MCP consists of 4 molecular components each of which is an independent prognostic marker after adjusting for RTOG RPA class. First, we include a comprehensive, 10 assay analysis of the *MGMT* promoter which more robustly predicts outcome compared to the standard single assay used in prior glioma trials [38]. Second, refinement of a gene expression (mRNA) classifier based on 19 genes that expands on a prior mRNA-based gene predictor [39]. Third, we have incorporated *IDH1* mutation status, a well-known genetic prognostic marker in gliomas [40]. As a fourth and final molecular component, an optimal set of gene promoters from the glioma CpG Island Methylator Phenotype (G-CIMP) [41] signature was selected to include 6 gene assays. Patients are divided in 1 of 3 risk groups based on the number of methylated sites.

The combination of these 4 molecular classifications resulted in 72 possible risk groups (the product of 3 *MGMT*, 4 mRNA, 2 *IDH1*, and 3 CIMP) that were then subjected to classification partitioning resulting in 4 molecular-prognostic (MP) groups. These 4 MP groups were then combined with the 3 RTOG RPA classes (12 risk groups total, the product of 4 MP and 3 RPA) and partitioned again into 4 resulting molecular-clinical prognostic (MCP) classes. The MCP

provides robust survival classification of patients with GBM. We propose to further validate it using patients from the current trial.

6.0 Patient Eligibility

Inclusion Criteria:

6.1 All patients must have histological proof of glioblastoma or gliosarcoma (WHO Grade IV) adapted RPA class III, IV, or V.

6.2 All patients must be ≥18 years of age.

6.3 All patients must sign informed consent verifying that they are aware of the investigational nature of this study in keeping with the rules and policies of M.D. Anderson Cancer Center. The only acceptable consent form is the one approved by M.D. Anderson IRB.

6.4 All patients must have a baseline Mini Mental Status Examination score ≥21.

6.5 All patients must have a KPS ≥70.

6.6 All patients must be eligible to have either IMRT or IMPT as determined by the study radiation oncologist.

6.7 All patients must be able to undergo MRI with and without contrast with a glomerular filtration rate (eGFR) greater than or equal to 30 mg/min/1.72 m^2.

6.8 All patients must have adequate liver, renal, and hematologic function within 14 days of registration as defined by Aspartate Amino Transferase (AST)/Alanine Amino Transferase (ALT)/Alkaline Phosphatase < 3 times normal, creatinine ≤1.7 mg/dl, BUN ≤ 35mg/dl, absolute neutrophil count ≥1,800 cells/mm^3, Hemoglobin ≥ 10 g/dl, and platelet count > 100,000.

6.9 All patients must be able to adequately read, write and speak to participate in the cognitive and quality of life assessments. However mild to moderate deficits in these functions due to tumor are allowed.

Exclusion Criteria:

6.10 Patients will be excluded if they are not planning to receive concurrent temozolomide.

6.11 Patients will be excluded if they have had prior radiation to the brain.

6.12 Patients will be excluded if they have had prior surgical resection of brain for other brain tumors.

6.13 Patients will be excluded if they are pregnant as assessed by serum b-HCG. A serum b-HCG test will be performed no greater than 14 days prior to study registration for women of childbearing potential.

6.14 Patients with gliomatosis will be excluded.

6.15 Patients with Glialdel (BCNU) implanted wafers will be excluded.

6.16 Patients weighing greater than 136 kilograms will be excluded.

7.0 Treatment Plan

7.1 Eligible patients will be randomized in equal numbers to each treatment arm using CORe. Randomization will be stratified using the following factors:
- 7.1.1 RPA class (III or IV vs. V)
- 7.1.2 Mini Mental Status Examination score (21-26 vs. 27-30)
- 7.1.3 Age (less than 65 vs. 65 or older)

7.2 Following randomization, insurance pre-authorization will be obtained for the specified treatment modality. If a patient's insurance will not cover payment for the assigned treatment arm, that patient will be removed from the study and will be treated off protocol.

7.3 Radiation target definition for glioblastoma as follows. GTV defined as tumor cavity and any T1 tumor enhancement. CTV will include GTV + 2 cm margin customized to include FLAIR enhancement (if thought by the radiation oncologist to be tumor) and exclude bone, fascia, and other anatomical barriers. PTV-50 will include CTV + 3-5 mm and will be treated to 50 Gy in 30 fractions. PTV-60 boost volume will include GTV + 3-5 mm and will be treated to 60 Gy in 30 fractions.

7.4 For patients randomized to IMRT, treatment will be planned using Pinnacle software system. Planning will be based on non contrast CT images obtained at time of simulation in addition to MRI scan. Treatment will be delivered using linear accelerator. Fractionated radiation will be delivered daily M-F with weekends off for all patients. IMRT plans use a configuration of five to seven isocentric 6-MV photon beams delivered in a step-and-shoot technique. For inverse planning specified dose constraints are given to organs at risk including the brainstem, spinal cord, optic chiasm, optic nerves, and cochlea.

7.5 For patients randomized to IMPT treatment planning will be conducted using the Varian Eclipse system. The same target delineation and expansions will be used as detailed above for IMRT. Treatment will then be delivered using the 250 MeV synchrotron (Hitachi Ltd. Power Systems, Ibarakiken, Japan) at the Proton Therapy Center at MD Anderson Cancer Center. Treatments will be delivered as once daily fractions, 5 days per week M-F with weekends off for all patients. IMPT may be planned using either multi-field optimization or single field optimization depending on the individual patient case. In single field optimization each field is optimized to deliver the prescribed dose to the target volume. Multi-field optimization uses simultaneous spot optimization and has been previously described [42]. Additionally if passive scatter is utilized, physical aperatures or compensators are utilized to modify the intensity of the beam. Beam angles are similar to those used for 3D proton therapy. For purposes of inverse planning specified dose constraints are used for organs at risk as in IMRT planning. The RBE for proton irradiation is set at 1.1. Thus the dose unit, Gy (RBE) is proton dose in Gy x RBE of 1.1.

7.6 Dose limitations to critical structures. Below is a list of dose constraints to critical structures. Every effort should be made to achieve these normal tissue constraints.

Brainstem	V60Gy<0.01cc and V55Gy <0.5cc and V30 <33%
Brain	V30Gy<50%
Chiasm	Max dose<54Gy
Cochlea (Left)	Max dose<45Gy and mean < 30 Gy
Cochlea (Right)	Max dose<45Gy and mean < 30 Gy
Eye (Left)	Max dose<40Gy and mean < 30 Gy
Eye (Right)	Max dose<40Gy and mean < 30 Gy
Len (Left)	Max dose<5Gy
Len (Right)	Max dose<5Gy
Optic Nerve (Left)	Max dose<54Gy
Optic Nerve (Right)	Max dose<54Gy
Hippocampus	No defined dose constraint. See below.

In addition, bilateral hippocampal contours will be manually generated on the fused planning MRI CT image set by the treating physician. These contours should be generated as performed in RTOG 0933.

8.0 Pretreatment Evaluation

8.1 A history and physical, including detailed neurological exam and recording of Karnofsky Performance Status (KPS) will be performed on all patients enrolled.

8.2 Patients will be referred for a detailed neuropsychological evaluation by the neuropsychology team. Neuropsychological evaluation will include the battery of standardized tests and measures listed below which will comprise the primary instruments of interest for the purposes of this study. This standardized battery is routinely used to assess patients with intracranial tumors at MDACC. The following tests were selected because they are widely used, standardized psychometric instruments that have been shown to be sensitive to the neurotoxic effects of cancer treatment in other clinical trials [19, 43, 44]. Normative data have been published for all tests that take into account age, education and sex, where appropriate. These tests were also selected to minimize practice effects on repeated administration. The memory test has six alternate forms and the verbal fluency test has two alternate forms. Additional tests and measures will be administered to patients at the discretion of the attending neuropsychologist based on clinical need for each individual patient. The neuropsychological evaluation will take approximately 2 hours of face-to-face contact with the patient to complete all of the testing. All reasonable effort will be made to complete testing prior to the start of radiation therapy. However, in cases where this is not possible evaluation will be completed within the first 5 fractions of radiation treatment.

Cognitive Function Measured	Test
Memory	Hopkins Verbal Learning Test-Revised[45]
Psychomotor Speed	Trail Making Test Part A[46]
Executive Function	Trail Making Test Part B [46]
Executive Function	Controlled Oral Word Association[47]

Symptom/QOL Measures	Test
Symptom	MD Anderson Symptom Inventory Brain Tumor (MDASI-BT) [48]
Quality of Life	EORTC QLQ C30/BN20 [49]

8.3 Laboratory studies including CBC, liver function tests including AST, ALT, alkaline phosphatase, electrolytes, and Blood Urea Nitrogen (BUN)/Serum creatinine.

8.4 Routine MRI of the brain with and without contrast and including diffusion weighted images must be obtained prior to initiation of radiation and no greater than 4 weeks prior to study registration and reviewed by radiology to identify all measurable disease. This scan will be considered the baseline scan (time 0).

9.0 Evaluation During Study

9.1 A history and physical exam will be performed at two month intervals for a total of 24 months of follow up after the completion of the assigned treatment (±30 days). Note the first evaluation after radiotherapy will frequently be performed approximately 4 weeks after completion of radiotherapy and then the study will continue with history and physical exam at 2 month intervals.

9.2 Neuropsychological testing will be performed at each follow up visit, up to two years post radiation treatment. Reasonable effort will be made to complete this testing prior to patients meeting with their physicians and receiving information about the status of their disease.

9.3 Routine MR imaging of the brain performed with and without contrast will be obtained at each follow up visit at 2 month intervals (±30 days) until recurrence or up to two years post radiation treatment. Note the first evaluation after radiotherapy will frequently be performed approximately 4 weeks after completion of radiotherapy and then the study would continue with follow-up imaging at 2 month intervals. These post-treatment scans will be analyzed and compared to baseline scans for identification of regions demonstrating changes in contrast enhancement including size, heterogeneity and rim thickness. Qualitative estimation of associated T2-FLAIR changes will also be evaluated. Early stages of malignant gliomas have demonstrated decreased water diffusion. Routinely obtained diffusion weighted images and reconstructed ADC maps will be analyzed to see if there is a difference between pre- and various post-treatment scans. Based on contrast enhancing imaging features, manually selected regions of interest on ADC maps will be

quantitatively analyzed, normalized to contralateral unaffected brain parenchyma and compared on serial scans. Similarly DTI maps and cognitive functions will be correlated.

9.4 Medication usage (specifically steroid dose, narcotic pain medications, antiepileptic agents, psychostimulants) will be recorded. Steroid doses will be adjusted based on clinical and radiographic criteria.

9.5 Requirements for more frequent evaluation will be documented. Data on unscheduled follow-ups will also be documented.

9.6 Research blood products will be collected within the first five fractions of treatment and at each evaluation period as stated above. At each interval, 2 tubes (10 mL) of serum (using "red" top tube, no additive) and 1 tube (10 mL) of whole blood (EDTA additive, "purple" top tube) will be collected.

10.0 Criteria for Response and Toxicity

10.1 Definition of primary endpoint:

10.1.1 Time to cognitive failure on any of the 6 primary variables from the pre-specified cognitive tests (HVLT-R total recall, HVLT-R delayed recall, HVLT-R delayed recognition, TMT Part A or Part B, COWA) with failure defined as a decline that meets or exceeds the reliable change index (RCI) for each cognitive test variable. A cumulative incidence approach will be used to estimate median time to cognitive failure in order to account for the competing risks of disease progression and death. Patients experiencing disease progression or patients that died prior to experiencing cognitive failure will be considered as having had a competing event. Progressive disease frequently causes cognitive decline, and the goal of this study is to assess the impact of the radiation treatment itself on cognitive decline.

10.2 Definitions of secondary endpoints:

10.2.1 Local control and distant control in the brain will be measured by contrast-enhanced brain MRI scan using Response Assessment in Neuro-Oncology (RANO)Criteria, as follows [50].

10.2.1.1 Complete Response (CR): Requires all of the following 1) complete disappearance of all enhancing measurable and non-measurable disease sustained for a minimum of 4 weeks; 2) no new lesions; 3) stable or improving non-enhancing (T2/FLAIR) lesions; 4) patients must be off corticosteroids (or on physiologic replacement doses only); and 5) stable or improved clinically.

10.2.1.2 Partial Response (PR): Requires all of the following: 1) ≥50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; 2) no progression of non-measurable disease; 3) no new lesions; 4) stable or improved non-enhancing (T2/FLAIR) lesions on the same

or lower dose of corticosteroids compared with the baseline scan; 5) stable or improved clinically.

10.2.1.3 Progressive Disease (PD): Defined as any of the following 1) ≥25% increase in the sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing dose of corticosteroids; 2) significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with baseline or best response not caused by comorbid events (i.e. radiation therapy, demyelination, ischemic injury postoperative changes); 3)any new lesion; 4) clear clinical deterioration not attributable to other causes apart from tumor (i.e. seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, or decrease in corticosteroid dose); 5) failure to return for evaluation due to death or deteriorating condition; 6) clear progression of non-measurable disease.

When making the diagnosis of progressive disease it is import to recognize the possibility of pseudo-progression, especially if the patient is clinically stable. In those situations, treatment should continue and status of local control should be evaluated with a repeat interval scan. If the subsequent scan confirms progression then the date of progression should be backdated to the original scan suggesting progression.

10.2.1.4 Stable Disease (SD): Requires all of the following 1) does not qualify for complete response, partial response, or progression; 2) stable FLAIR/T2 lesions on corticosteroid dose no greater than at baseline; 3) clinical status stable.

10.2.1.5 For local control, PD is considered local failure, or stable disease with deterioration of the neurological examination with a grade III or worse toxicity on the CTCAE v.4.0 scale (see Appendix). All others (CR, PR, asymptomatic SD) are deemed success.

10.2.2 Overall survival will be measured from registration until death. After 2 years of follow-up event monitoring will be used.

10.2.2.1 Patients with unknown vital status will be censored at the date of last visit or MRI scan.

10.2.3 Quality of life will be measured at each two month interval follow up visit out to two years using the EORTC QLQ C30/BN20 and the MD Anderson Symptom Inventory Brain Tumor (MDASI-BT).

10.2.4 At each two month interval follow up visit out to 2 years all six pre-specified cognitive test variables will be assessed. The pattern of cognitive change in memory, executive function, and processing speed will be assessed at each time point. The composite cognitive function

score will be determined by averaging standardized Z-scores from all pre-specified cognitive test variables (5 out of 6 are required to calculate a composite score).

10.2.5 MRI imaging including diffusion weighted images (DWI) and reconstructed apparent diffusion coefficient (ADC) maps will be analyzed for differences between pre- and post-treatment scans. They will also be analyzed for differences between the two treatment modalities.

10.2.6 Diffusion tensor imaging (DTI) will be analyzed for correlation to the cognitive changes and for differences between the two treatment modalities.

10.2.7 Pre-treatment factors of RPA class and MMSE will be assessed for predictive determination of local and distant control and cognitive outcome in each treatment arm.

10.2.8 Assessment will be made for correlation between location of primary lesion, total volume of intracranial disease, and cognitive outcome for each of the treatment arms.

10.2.9 The relationship between MGMT promoter methylation status and cognitive and local control outcomes will be assessed.

10.2.10 Post treatment side effects will be recorded at each follow up visit out to two years. Toxicity will be recorded according the Common Terminology Criteria for Adverse Events v4.0.3 for Nervous System Disorders. Only grade 3 and above toxicity that is directly related to therapy will be required to be documented. Pretreatment symptoms should not be considered as toxicity related to the treatment and are not required to be documented unless the symptoms worsen as a result of therapy.

10.2.11 Dosimetric parameters such as dose to the hippocampus will be analyzed for relationship with cognitive and local control outcomes.

10.3 Evaluation of correlative markers

10.3.1 Genetic markers: DNA will be extracted within the first five fractions of treatment in the laboratory of the Study Chair. Apo E (i.e., Apo E2, Apo E3, and Apo E4) genes will be analyzed for single nucleotide polymorphisms (SNPs) either by Taqman or direct sequencing.

10.3.2 Inflammatory Markers: Serum specimens collected within the first five fractions of treatment and at each follow-up visit will be analyzed using commercially-available ELISAs from R&D Systems, Inc. for the following inflammatory biomarkers: interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNFα). These markers will be assayed in the laboratory of the Study Chair.

10.3.3 Hormone and Growth Factors: Serum specimens collected within the first five fractions of treatment and at each follow-up visit will be analyzed using commercially available Enzyme Linked Immunosorbant Assays (ELISAs) for the following hormone and growth factors: glucocorticoids (e.g., cortisol), gonadal steroids (e.g.,

estradiol, testosterone, progesterone), growth hormone, human chorionic gonadotropin (hCG), insulin-like growth factor-1 (IGF-1), and neuronal growth factor (NGF). These assays will be performed in the laboratory of the Study Chair.

10.3.4 A portion of the serum and DNA will initially be analyzed as described above. According to patient consent information, the remaining body fluid biospecimens will be stored as de-identified frozen specimens in locked storage at -70ºC in the laboratory of the Study Chair. As new protocols are developed they will be presented for IRB review and approval.

10.3.5 Return of Genetic Testing Research Results: Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians. If at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a Food and Drug Administration (FDA) Clinical Laboratory Improvement Amendments (CLIA)-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

10.3.6 For analysis of MCP class, all assays will be performed on residual formalin-fixed, paraffin embedded (FFPE) tissue remaining after pathological diagnosis. Representative hemotoxylin and eosin sections will be used to identify tumor content by an M.D. Anderson Neuropathologist. FFPE-derived RNA and DNA will be prepared using the MasterPure Complete DNA and RNA purification kit (Epicentre Biotechnologies, Madison, WI) following deparaffinization using Citrisolve (Amity International, Anderson,SC). *MGMT* promotor methylation and G-CIMP status will be determined by bisulfite conversion of DNA and real-time PCR amplification. *IDH1* status will be determined from the medical record or by direct sequencing when necessary. 19-gene mRNA signature will be determined by real-time PCR following reverse transcription of mRNA

11.0 Criteria for Removal from the Study

11.1 Analysis will be by intention-to-treat and those patients who withdraw from the study after randomization, but prior to receiving treatment will be tracked to ensure there is no bias introduced into the study.

11.2 Patients who do not complete the assigned treatment will be recorded and followed. These patients can be treated by best medical therapy as per the judgment of the treating physicians.

12.0 Statistical Considerations

12.1 Randomization procedure: A stratified block randomization procedure will be used. Randomization will be performed using CORe. The randomization strata are as defined above in section 7.0, and the block size will be 6. Patients who withdraw from the study after randomization, but prior to receiving treatment will be considered a cancel and replaced.

12.2 Sample size: With IMRT the cognitive function failure rate at 4 months is 45%, based off of comparative analyses of the cognitive failure rate of RTOG 0614 and compared to the cognitive impairment seen on RTOG 0525; we hope to demonstrate that IMPT can achieve a cognitive function failure rate at 4 months of only 30%. We assume the time to cognitive failure in each treatment arm follows an exponential distribution. A cognitive failure rate of 45% at 4 months then implies a median time to cognitive failure of 4.6 months, while a cognitive failure rate of 30% at 4 months implies a median time to cognitive failure of 7.8 months.

We will use a 1-sided significance level of 0.20 as suggested by Rubinstein et al. [51]for phase II screening trials. We expect to enroll 2 patients per month, and we will randomize 60 evaluable patients (30 to each treatment arm). We will have 80% power to detect an improvement in cognitive failure at 4 months from 45% in the IMRT arm to 30% in the IMPT arm. We expect to observe 43 events, and the analysis will be performed once we have observed these events. We define evaluable patients as those who have received the assigned treatment *and* completed baseline and at least one follow-up neurocognitive testing. We expect we will need an over accrual of 33% to account for those patients not evaluable. Therefore the target total enrollment sample size is 90 patients to accrue a total of 60 evaluable patients. We expect to observe 43 events, and we expect the trial to take 41 months to observe these events.

12.3 Primary Analysis: The analysis will be performed on the intention-to-treat principle. Considering those patients who are not evaluable as treatment failures. We will use the methods of Gooley et al. [52]to estimate the cumulative incidence of cognitive failure in each treatment arm, considering progressive disease and death before cognitive failure as competing events. We will estimate the cumulative incidence of cognitive failure at 4 months with 95% confidence intervals. We will use the methods of Fine and Gray [53]to test for a difference between treatment arms with respect to the cumulative incidence of cognitive failure, considering progressive disease and death before cognitive failure as competing events. Our model will include treatment arm and the stratification factors used at randomization.

12.4 Secondary Analysis:

We will repeat the primary analysis on only those patients considered evaluable. All the secondary analyses described below will be performed using all patients as well as using only evaluable patients. We will estimate the cumulative incidence of local failure using the methods of Gooley et al.

considering death as a competing event. We will model the time to local failure using the methods of Fine and Gray to test for differences between treatment arms, considering death as a competing event. Our model will include treatment arm and the stratification factors used at randomization, as well as selected dosimetric parameters. We will similarly analyze time to distant failure.

We will use the product limit estimator of Kaplan and Meier [54] to estimate overall survival stratified by treatment arm. We will also use Cox proportional hazards regression [55]to model overall survival as a function of treatment arm and the stratification factors used at randomization.

We will use descriptive statistics to summarize by treatment arm the quality of life data at each assessment time. We will also use boxplots to summarize the quality of life data by treatment arm at each assessment time. We will model the quality of life data using mixed effects regression methods with repeated measures. The model will include treatment arm, selected dosimetric parameters, baseline cognitive function, location of the primary tumor (left vs. right hemisphere, if bilateral disease is present, location will be determined by the hemisphere with highest burden of disease), and the stratification factors used at randomization as fixed effects and patient as a random effect. We will similarly analyze the cognitive tests. For nearly all the prior mentioned analyses we will also plan to conduct an as-treated analysis.

We will tabulate by treatment arm the adverse events by grade and relationship to treatment.

We will use logistic regression methods to model the logit of the probability of neurocognitive decline as function of ApoE (i.e., Apo E2, Apo E3, Apo E4) genotyping, inflammatory markers (i.e., IL-1, IL-6, TNF-α), and hormone growth factors (i.e., glucocorticoids, gonadal steroids, growth hormone, human chorionic gonadotrpin, insulin-like growth factor-1, neuronal growth factor).

Determination of MCP class will be determined by RPA analysis using results of MGMT, *IDH1*, G-CIMP, and mRNA assays as well as RTOG RPA class. We will use descriptive statistics to report class distributions overall and by treatment arm. Survival by classes will be visualized on Kaplan/Meier plots, compared by the logrank test. The Cox proportional hazards regression will be used to model MCP classification, adjusting for treatment arm and stratification factors.

13.0 Data and Protocol Management

13.1 To ensure protocol compliance, the principal investigator, treating radiation oncologist, study neuroradiologist and research nurse will review the patient data and MRI films prior to randomization. All required pretreatment data

should be available before a decision to enroll the patient on the protocol is made.

13.2 All data with the exception of the neuropsychological data will be collected by the research nurse in charge of the protocol. This includes pretreatment, treatment, and post treatment data. The neuropsychological data will be collected by members of the Section of Neuropsychology. Dr. Wefel will maintain a study specific database containing the cognitive outcomes. The medical and neuropsychological databases will be integrated by the study statistician at the time of analysis and/or to prepare for MDACC DSMB review. The study chairman will act as the final arbitrator of all study parameters should a difference of opinion exist. Patients who meet eligibility criteria will be registered in CORe.

13.3 De-identified DICOM images and matched clinical variables will be shared with Dr. Thomas Yankeelov, PhD, University of Texas at Austin, Biomedical Engineering, TX, US; using secured M.D. Anderson Box cloud. The purpose of this collaboration is to spearhead an effort to leverage advanced imaging modalities, including multi-parametric and functional MRI to identify clinically applicable non-invasive means of characterizing radiation-induced normal brain injury and subsequent prediction of patterns of cognitive side effects.

13.4 De-identified DICOM images and matched clinical variables will be shared with Dr. Arvind Rao, PhD, University of Michigan, Department of Computational Medicine & Bioinformatics; using secured M.D. Anderson Box cloud. The purpose of this collaboration is to spearhead an effort to leverage advanced imaging modalities, including longitudinal multi-parametric and functional MRI to identify clinically applicable non-invasive means of characterizing patterns of tumor response to radiation treatment.

13.5 Imaging data may be shared with Björn Hårdemark at RaySearch Laboratories in order to analyze using advanced imaging tools. All patient data will be de-identified according the RSNA's MIRC protocols and using MIRC specified software. This tool de-identifies all DICOM tags that can identify a patient as an individual by replacing them with a randomly generated number or discarding their value all together. Following de-identiftication, the data is compressed and uploaded to a secure BOX repository (supported by MD Anderson), and collaborators will be given instructions on how to access the data. MD Anderson will have primary oversight over data and any future use of data must be in the context of an IRB approved protocol.

14.0 Reporting Requirements

14.1 Radiation using either photon or proton technique has known associated risks, including tumor swelling, neurological decline, edema, and radiation necrosis. Nonetheless, radiation is considered standard of care. Adverse treatment reactions will be reported to the IRB. Standard monitoring procedures as noted above to detect and treat postoperative complications will be followed.

14.2 All attempts will be made to preserve patients' confidentiality. Patient records will be kept electronically or in secure file cabinets and handled only by responsible personnel.

14.3 Study progress and analyses of safety data will be presented to the MDACC DSMB on an annual basis, or as requested.

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