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CONTRACTING ORGANIZATION: Unviersity of Pennsylvania
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14. ABSTRACT

This report describes continued work on the award "Neurocognitive Effects of Radiotherapy", which examines the neurocognitive and imaging impact of proton therapy for patients will low grade glioma and base of skull meningioma. A total of 59 subjects (patients and control) have been enrolled, 12 of whom have enrolled in the past year. All subjects have completed a 4-5 hour neurocognitive testing assessment at baseline by Dr. Carol Armstrong. In addition, all subjects have completed a 1 hour standard MRI as well as additional testing including diffuse tensor imaging (DTI), perfusion and diffusion. The majority of patients have completed baseline and at least two additional time-points in regards to both neurocognitive testing and MRI. Eight patients have completed neurocognitive and imaging evaluation at all planned timeponts, and preliminary data analysis is provided in this report. Local control and overall survival remain 100% in both testing cohorts. Although data are preliminary, neurocognitive results suggest that, on measures of verbal retrieval from long-term memory (retrieval after interface and retrieval after time), patients treated with proton therapy show post-treatment decline, but a stronger recovery and larger memory capacity compared to those treated with photons. Implicit cognition was tested via cerebellar tests, and results were compared for 20 patients and 20 controls. Control patients appeared to perform better than patients after proton therapy on specific cerebellar tests, including Timing Functions Test and Serial Response Test, although the performance of the two groups on the Audiovisual Attentional Shift Test did not differ. These tests have not been used previously within the proton radiation population, and appear to be promising tools for elucidating differences in implicit cognition in this and future studies. Imaging analysis has been carried out independently from neurocognitive analysis. Preliminary imaging data demonstrate that hippocampal imaging changes appear to correlate well with tumor location (preservation of the contralateral hippocampus after radiation). Review of FA data suggest that midline BOS tumor treatment does not result in hippocampal changes on FA, but that treatment of brain parenchymal tumors may cause differences on FA based on laterality of the tumor and the radiation. Similar observations have been made with regard to blood perfusion based on rCBV values. We have established tools within our department that will assist future MRI interpretation and correlation with radiation dose. A component (10%) of this award supported the Walter Reed Army Medical Center scientists. Dr. Michelle Alonso-Basanta is Principle Investigator for this. Susan Prendergast is the Clinical Research Coordinator managing the associated IRB-approved protocol. Dr. Christine Hill-Kayser is the Project Manager for this section of the award. Further budgetary details are outlined in the attached document.

15. SUBJECT TERMS

Radiation Oncology, Proton Therapy, Image-Guided Radiotherapy, Neurocognitive, MRI

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October 10, 2015

To
Anthony M. Pacifico, Ph.D
Portfolio Manager, Medical Imaging Technologies
IPA, Battelle Memorial Institute
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1054 Patchel Street
Fort Detrick, Maryland 21702

RE: USAMRAA award W81XWH-09-2-0174– update of timelines and budget

Phase six of the award focuses on neurocognitive studies and imaging. This study expands on previous work and looks to specifically compare proton therapy with advanced conventional therapy such as Intensity Modulated Radiation Therapy (IMRT) for patients with low grade glioma of the brain and for patients with base of skull (BOS) meningioma.

Current status- Over the past year, Michelle Alonso-Basanta, MD, has continued as Principle Investigator of this protocol. We have completed the development of a clinical protocol that covers the entire project, and the protocol was revised for scientific and operational clarity in 9/2011. Early in the second year, eligibility requirements were updated to include patients with diseases of different histologies, and these changes were approved by both the Penn IRB and the DOD Review Board. The minimum radiation dose was also decreased to 45 Gy. These changes have facilitated our meeting target accrual on time. A total of 60 patients and control have been enrolled (35 in the radiation cohort and 25 control subjects). Accrual over the past year was 12 patients.

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Although we have had a fruitful accrual of patients over the last few years, particularly in cohort 1 for the skull base, cohort 2 has had a much slower accrual for patients. Causes are variable and most are attributed to time required, claustrophobia and stress of diagnosis. In addition, given the limited histology associated with this cohort, many patients including grade II meningiomas, and grade III gliomas, were not eligible. Regardless, this study has generated great interest both in other departments at the University of Pennsylvania, as well as from other prominent institutions.

Given that we have not completed all the time points of the study for the patients enrolled, we requested a no cost extension in order to complete the remaining time points for those patients accrued so that we may have a more robust analysis at the completion of all study points, with a predicted end date for those time points in September 2017. Accrual of new patients will halt at 35.

Below is a breakdown of accrual by year and cohort.

Year	2009-2010		2011		2012		2013		2014		2015	
	M	F	M	F	M	F	M	F	M	F	M	F
Cohort 1	0	0	0	0	2	2	1	4	2	8	3 36/73	3 29/67)
Cohort 2	0	0	0	2	0	2	1	2	1	2	0	0
Control	0	0	1	1	3	0	2	5	4	7	0	2
	M=male											
	F=Female											
	(xx)=age or age range											
STUDY TOTAL RT SUBJECTS = 35 as of 10/2015												
	M	F										
Cohort 1	8	17										
Cohort2	2	8										
RT total	10	25										
STUDY TOTAL CONTROL SUBJECTS = 24 as of 10/2015												
	M	F										
Control	10	15										

All patients have completed a 4-5 hour neurocognitive testing assessment at baseline by Dr. Carol Armstrong. In addition, all patients have completed a 1 hour standard MRI as well as additional testing including diffuse tensor imaging (DTI), perfusion and diffusion. The majority of patients have completed baseline and at least two additional time-points in regards to both neurocognitive testing and MRI. Preliminary results are presented as part of this report.

2011 Q4 – enrollment initiated
2012 Q1 until 2014 Q2- continue enrollment and studies with relaxation of enrollment criteria
2014 Q2- continue enrollment and studies of low grade glioma. Complete BOS study
2014 Q3- until 2015 Q2- continue enrollment and studies
2015 Q3- complete study
2017Q3- No cost extension to complete testing of all enrolled patients

An updated version of the budget is attached. Please do not hesitate to contact me directly with any questions or concerns.

Sincerely yours,

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Award Number: W81XWH-09-2-0174

Introduction

The overall goal of this multi-year research project in collaboration with the Walter Reed Army Medical Center is to develop the necessary technology to make the proton facility in Philadelphia the most advanced proton radiotherapy center. Award # W81XWH-09-2-0174 comprises phase 6 of this endeavor and consists of the following clinical study:

Neurocognitive protocol

Preliminary data suggest that regions of the normal brain exposed to radiation doses that has otherwise been regarded as safe and not limited by current radiation treatment planning may contribute to the risk of late neurocognitive injury. Radiation dose-dependent subclinical vascular effects have been reported in irradiated normal brain tissue and have been hypothesized to be a potential mechanism of action. Direct neuronal injury is another potential mechanism of injury. **Purpose:** 1) To estimate the degree of cognitive loss following radiation therapy. 2) To determine if clinical variables (including medications, age, mood disturbance, fatigue, chemotherapy, neurological and cerebrovascular comorbidities) correlate with memory decline as measured by neurocognitive testing in a prospective longitudinal study using a similar neurocognitive test battery. 3) To describe radiotherapy dose-related changes in vascular perfusion, in spectroscopic parameters of neuronal injury, and in changes in the degree and directionality of tissue water diffusivity (diffusion tensor imaging). 4) To correlate the MRI findings in regions of interest (ROIs) with neurocognitive changes, focusing initially on changes in memory. **Methods:** Eligible subjects will include patients with tumors (benign or malignant) of the skull base or patients with low grade glioma or meningioma who require radiotherapy. 10 subjects receiving photon treatment plans and 20 subjects receiving proton treatment plans with tumors (benign or malignant) involving the base of skull and a total of 40 patients with low grade glioma or meningioma will be prospectively enrolled. Baseline perfusion, spectroscopic, and diffusion MRI imaging of the brain utilizing established techniques will be used to identify and characterize the regions of interest (ROI) anatomically adjacent to the regions of intended high dose irradiation. The MRI data for the ROIs will be registered with the radiotherapy treatment planning CT in order to create a single volume of data where each voxel corresponds to a vector containing the multi-parametric information. Subsequent repeat MRI imaging will be approximately at 1.5, 6, 12, and 24 months following completion of the radiotherapy for patients. Both cohorts will repeat standard neurocognitive evaluation at approximately 1.5, 6, 12 and 24 months following completion of radiotherapy. A normal, control (non-diseased) group will have 70 subjects. This normal group will not have radiotherapy. This group will only have neurocognitive evaluation at enrollment (baseline) and approximately 3 months from baseline. **Analysis:** Neurocognitive domains will be evaluated at the designated time points. These will include: verbal and visual memory; immediate attention, working memory, and processing speed; executive functions and affect and depression. The primary analysis will be to evaluate within-patient changes from baseline to one year.

Body

The Hospital of the University of Pennsylvania, in collaboration with Walter Reed Army Medical Center, is building the most advanced cancer treatment facility in the world. This will be a fully-integrated facility utilizing state-of-the-art imaging and conformal treatment techniques including proton radiotherapy. Research projects with the intent of full implementation of end products are required to reach the full potential of proton therapy. In the original statement of work first of five planned projects were identified, to be implemented on a yearly basis to provide the most advanced cancer treatment facility in the world. Each of these projects will help advance proton therapy worldwide and result in measurable benefits. The projects identified were:

(1) Multi-leaf collimator (MLC) for use on proton therapy gantries

(2) Cone Beam CT on the Gantry for localization of target volumes

(3) Proton Radiography to determine dose and stopping power of various tissues

(4) Positron Emission Tomography (PET) imaging on the gantry to evaluate dose deposition within tissues irradiated

(5) Scanning proton beam using adaptive radiotherapy techniques based on implementation of MLC, Cone Beam CT, PET imaging.

A major aim of the entire project is to provide the most advanced radiation therapy to military personnel and their immediate families; the facility opened for patient treatment in January, 2010.

Much of this work has been initiated in earlier phases of this award. Phase 1 concentrated on designing and building a Multi-leaf collimator for use in proton therapy. Phase 2 focused on studying the optimal way to use scanned proton beams. The purpose of Phase 3 was to include the ideas of adaptive radiotherapy techniques and to define the role of imaging in proton therapy including the introduction of on-gantry cone beam CT (CBCT). The integration of these techniques, redefined as image guided proton therapy (IGPT) and adaptive proton therapy (APT) was a major aim of the phase 3 proposal. Phase 4 "Proton Therapy Dose Characterization and Verification" investigates the use of PET to verify dose distributions from proton beams as well as characterizing the radiobiological effect. Phase 5 "Development of Technology for Image-Guided Proton Therapy" is designed to bring to proton radiotherapy some techniques, such as cone-beam CT and Calypso localization, which are available in conventional radiotherapy.

The current work (phase 6) investigates the effect of radiotherapy using serial MRI imaging and a series of neuropsychological measurements on two groups of patients; (1) those with base-of-skull , and (2) those with low-grade gliomas or meningiomas.

2015 Annual Progress Report 0174:
Detection of Vascular and Neuronal Changes and their Correlation to Neurocognitive Changes following Proton and Photon Radiotherapy in Patients Receiving Skull Base and Brain Radiation.

This is the annual summary report of the UPCC #08310 in which patient enrollment began October 2011. Early in the second year, eligibility requirements were updated to include patients with diseases of different histologies as well as decreasing the minimum radiation dose to 45 Gy. This facilitated continued enrollment and plan for target accrual. We have attempted to minimize visits outside of the protocol requirements to assist most of the "out of town" patients to consider enrollment as we discovered that most patients did not want to make additional trips. Patients currently enrolled have commented that this has been helpful.
Attached is the current breakdown of enrolled patients ending on 9/30/15. A total of 60 subjects have been enrolled; 25 normal cohorts and 34 patients for cohorts 1 and 2 (31 protons and 3 photons). We have offered the study to one additional patient who will start treatment soon and we are awaiting consent.

The table attached includes all study procedures that have been completed as of 9/30/15. As mentioned above, we are awaiting consent on the last patient which would be in October 2015. Dates at each time point (per patient) include having completed neurocognitive testing assessment (by Dr. Carol Armstrong and her team) as well as MRI scans (standard MRI as well as diffuse tensor imaging (DTI), perfusion and diffusion).

We have been meeting every 2 months for the last 1.5 years and have begun to analyze and consolidate data for the first 8 patients who **have completed all 5 time points of the study**. In addition, the MRI data has been transferred and a process for overlapping radiation maps to the MRI and each subsequent sequence has been elucidated as of the summer of 2015. We have also started to correlate clinical endpoints to any neurocognitive changes noted per patient. Incorporation by cohorts is still ongoing.

We have met with our statistician and have agreed upon initial formatting for data acquisition. Below is a very preliminary evaluation of the first 8 patients that have completed all time points.

Clinical Update: Preliminary Results (9/30/15)

Table 1 includes patient demographics, dose, location and control with survival.

Patient Characteristics (early analysis 8 patients)			
		Cohort 1	**Cohort 2**
Age		31 (27-35)	46 (37-62)
M		2	0
F		2	4
Mean Dose (Gy)		64 (50.4-79.2)	54 (54)
Laterality			
	Midline	3	1
	Right	0	2
	Left	1	1
Location*			
	Base of Skull	4	1
	Frontal Lobe	0	2
	Temporal Lobe	0	1
	Parietal Lobe	0	1
Local Control		100%	100%
Overall Survival		100%	100%

Table 1. Patient Characteristics.*Radiation targets involving one or more locations are represented more than once.

More detailed information has been acquired for each case. The tables below include further information including organs at risk and toxicity.

Organs at Risk (early analysis 8 patients)					
			Cohort 1		**Cohort 2**
Average Max Dose to Organ at Risk[#] (Percent of Cases Above Dose Constraint*) in cGy					
	Brain		6729.8 (50%)		5661.5 (0%)
	Left Hippocampus		5264.5 (0%)		3318.1 (0%)
	Right Hippocampus		4160.0 (0%)		3656.3 (0%)
	Left Temporal Lobe		6665.9 (50%)		3540.7 (0%)
	Right Temporal Lobe		6159.0 (50%)		4157.9 (0%)
	Brainstem		6122.1 (0%)		4922.3 (0%)
	Spinal Cord		1757.1 (0%)		0.4 (0%)
	Optic Chiasm		5298.4 (0%)		4155.4 (0%)
	Left Optic Nerve		3498.8 (0%)		2931.8 (0%)
	Right Optic Nerve		3159.4 (0%)		3394.0 (0%)
	Left Lens		122.9 (0%)		229.8 (0%)
	Right Lens		175.9 (0%)		233.1 (0%)
	Pituitary Gland		6302.2 (100%)		3727.2 (50%)
	Left Lacrimal Gland		1255.7 (0%)		1643.7 (33%)
	Right Lacrimal Gland		1129.7 (0%)		607.4 (0%)
Average Mean Dose to Organ at Risk[#] (Percent of Cases Above Dose Constraint*) in cGy					
	Left Cochlea		2289.5 (0%)		799.4 (0%)
	Right Cochlea		2087.7 (0%)		1961.7 (25%)
	Left Eye		340.1 (0%)		353.8 (0%)
	Right Eye		207.1 (0%)		317.5 (0%)

Table 2. Organs at Risk. #The percent of patients with radiation doses exceeding the guidelines for a respective organ at risk was calculated using the available data of contoured structures from each patient plan. *Recommended dose constraints were obtained from QUANTEC (spinal cord, brain, optic chiasm, optic nerve, cochlea), RTOG 0225 & 0615 (eye/globe), RTOG 0539 (lens), Emami et al. 1991 (pituitary), and Parsons et al. 1996 (lacrimal gland). Average brainstem constraints in cohort 1 are higher than recommended as these patients are on a separate UPENN research study where dose maximum accepted was 6700 cGy.

We have also consistently accumulated toxicity data and graded as per CTCAE version 4.0 guidelines. Here is a representative of one patient. All patients have been data acquired in a database and can be compared over time.

		Common Terminology Criteria for Adverse Events v4.0 (CTCAE) Grade																									
		Fatigue	Anorexia	Confusion	Depressed level of consciousness	Cognitive disturbance	Headache	Vision changes	Hearing changes	Seizure	Dysarthria	Dysphasia	Facial muscle weakness	Other muscle weakness	Ataxia	Paresthesia	Insomnia	Depression	Constipation	Nausea	Vomiting	Diarrhea	Fecal incontinence	Urinary incontinence	Radiation dermatitis	Skin sensation	Alopecia
Baseline		0			0	0	1	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	
Time Since EOT	1.5 Months	0	0	0	0	0	1	1	0	0	0	1	1	0	1	1	1	0	0	1	0	0	0	0	0	0	1
	6.0 Months	1	0	0	0	1	1	1	0	0	0	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0
	12.0 Months							1						0													0
	24.0 Months	0	0	0	0	0	1	1	0	0	0	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0

Table 3. Example Clinical Toxicity Data for C1.001. Patients were monitored for signs and symptoms of toxicity due to RT at each of the study time points. Data were reported in the form of Common Terminology Criteria for Adverse Events v4., where values 1-4 represent a specific level of toxicity for a given organ or structure. Values of "0" within a given field indicate the absence of toxicity. Toxicities that were not present at baseline, but developed after RT, are highlighted in red. Yellow fields indicate toxicities that developed within the period of observation, but resolved by the 24 month clinical evaluation. Green fields indicate toxicity from pre-existing conditions, present before RT that did not change in severity over the course of the study. Information that was not available is labeled in gray. Abbreviations: EOT= End of Treatment.

Neurocognitive Testing: Preliminary Results (09/30/2015)

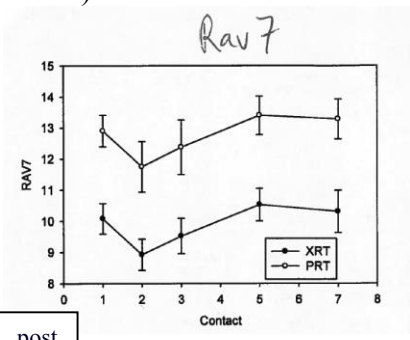
We adapted for this study four experimental tests of cognition that were found in prior studies to demonstrate activation in the cerebellum. In order to apply the tests that we proposed are cerebellar-sensitive, and to determine if they are useful cognitive markers of radiation injury, the tests should be stable in healthy controls over two time points. The cognitive markers reported in the progress note of 2014 (Timing Functions, Serial Response, and Audiovisual Attentional Shift)

included several indices that demonstrated stability across two time points in healthy controls (N=25) who were similar to patients (N=33) in age (p=0.40) and education (p=0.15).

Applying a Bonferroni correction to paired t-tests, one of the 40 cerebellar test indices met criterion for significant difference between the two time points in the healthy controls, due to a small practice effect. Other tests not meeting the error criterion but showing a trend demonstrated the same pattern of slightly better performance at the second test time. It is not unexpected that some practice effect would be found as the implicit cognitive system is very robust and can be functional even in the presence of cortical disease. The results over two test sessions indicate that the tests are reliable, and further analyses are needed to examine their role in measuring possibly declines following proton therapy in patients with brain tumors. In 2014 we provided preliminary findings on indices that changed over time in patients, and these analyses will add the control data in an updated mixed model.

Effects over Two Years in the Cognitive Markers of Radiation Injury

Complete data from baseline to two years was analyzed in a mixed model in 8 patients who received Proton therapy (PRT) and 45 brain tumor patients who received photon radiotherapy (XRT) from a historical dataset. The effects were examined before Protons and at three time points after Protons to two years, using a mixed effects model that included interval, therapy type, and individual random effects. We hypothesized that tests of verbal semantic memory would be sensitive to PRT, and that visual-perceptual memory would be insensitive to PRT. The hypotheses were confirmed: only the tests of retrieval of words from long-term memory (and not learning of the words) and the reaction time to retrieve semantic pictures (and not recall of perceptual figures) demonstrated the decline and recovery that were seen in patients who received XRT (Figure below).



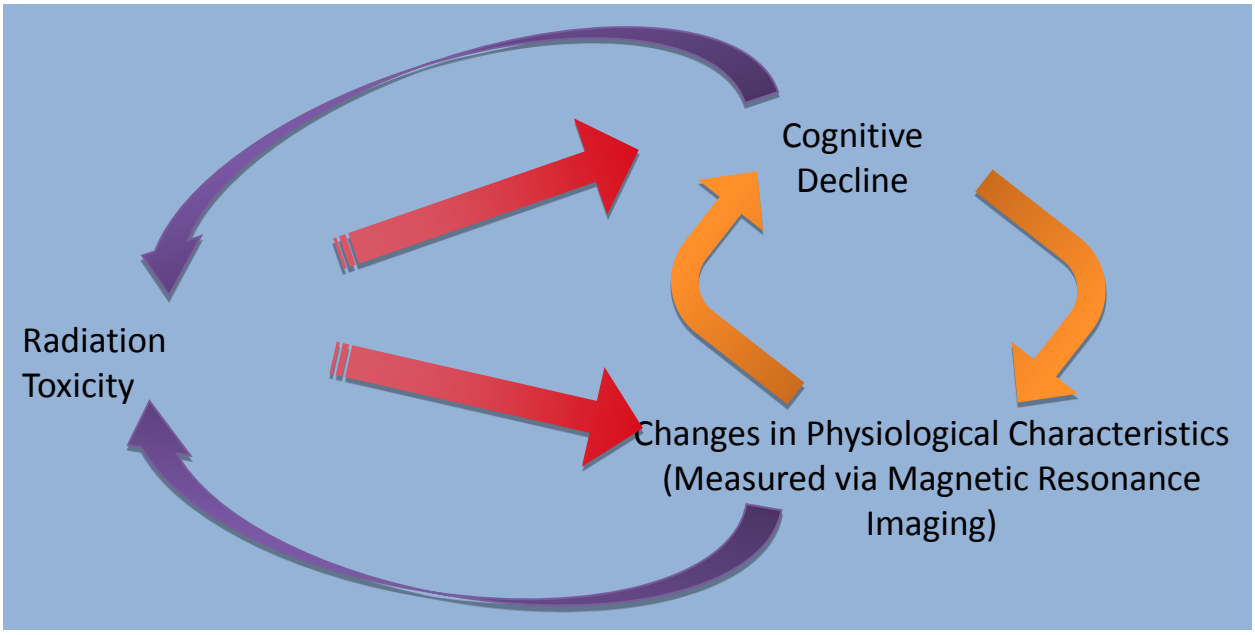
-XRT, 1 = 1.5m post
= 6 m post baseline, 5 = 1
y post baseline

Patients with PRT had stronger cognitive scores at baseline, which we attribute to their tumor characteristics. XRT patients' tumor were all in the parenchyma, but PRT patients' tumors were parenchymal and the base of skull. These results validate the use of the verbal semantic memory as cognitive markers of radiotherapy toxicity on cognition.

Patients receiving PRT had significantly (or trending) stronger cognitive scores in most of the test indices at baseline and throughout the two years of the study.

MRI Evaluation: Preliminary Results (09/30/2015)
Briefly, our hypothesis is that changes in physiology in the hippocampus, cerebellum and possibly other anatomic locations in the brain and base of skull, as measured by magnetic resonance imaging (MRI) will correlate with change in cognitive decline and to radiation-induced damage (Figure 2).

Figure 2



There are various parameters that can be measured with MRI and will briefly be described. As the signal is given off by relaxation of the excited protons in the body, we can obtain the diffusion tensor imaging (DTI) which includes parameters such as the Apparent Diffusion Coefficient (ADC) or the Fractional Anisotropy (FA). ADC is the mean diffusion outwards from a relative point and describes the cellular density of that voxel. The FA gives us unidirectional diffusion and allows us to measure the directional component of the diffusion. Alternatively, we can also obtain the Dynamic Susceptibility Contrast (DSC) which allows us to measure the Relative Cerebral Blood Volume (rCBV). This describes the blood volume in a region of interest and is an indicator of vascularization (or lack there-of) relative to white matter.
MRI images were collected before radiation treatment (baseline), and approximately 1.5, 6, 12, and 24 months after the completion of radiation therapy (RT). During a MRI study session, 19 pulse sequences were conducted, generating T1-weighted, T2-weighted, FLAIR, diffusion-tensor-

imaging (DTI), permeability, perfusion, and spectroscopic images. In general, MRI studies were performed on the same day of the cognitive testing, and took an hour to finish.

In 2015, we continued to scan new patients, and completed MR-parameter extraction of regions of interest (ROI), i.e., structural contours, for the eight patients who completed the 24 months follow-up neurocognitive study. Specifically, MRI data were first co-registered with one another, and then structurally co-registered to planning CT using rigid deformable image registration. Patient-specific structural contours, hence, were co-registered among all the images, allowing a single volume of data where each ROI corresponds to a vector containing the multi-parameter information at 1.5, 6, 12, 24 months after RT, including the dose statistics.

Previously, MR data were constructed independent of clinical data. The shortcomings were threefold: (1) inaccurate perfusion analysis, (2) inaccurate ROIs, (3) no dose statistics. First, perfusion analysis uses the artery input contralateral to the tumor site as the reference. It was not always clear where the tumor site was from the MR data alone, leading to inaccurate data analysis. Second, the standard brain atlas is a poor model for a tumor-involved brain, causing inaccurate mapping of ROIs. Last and most importantly, changes in MR parameters cannot be compared to the dose received, without clinical data.

For the eight patients, we created a new contour of corpus callosum, and measured its change in relative cerebral blood volume (rCBV) and in fractional anisotropy (FA) following RT. Generally, reduction in rCBV suggests vascular injury, while reduction in FA suggests neuronal injury. For each of the eight patients, we detected measurable vascular and neural change following RT. Together, percent reduction in rCBV and FA increases with radiation, suggesting dose-dependent vascular and neuronal damage.

Summary

This is an early example of cohort comparisons for our group as well as in comparison to historical controls. As more patients complete their time points, we hope this will add to our early analysis. Based on this data, we have initiated consideration for further funding to continue accrual, particularly for the parenchymal cohort (cohort 2). In addition, this has stimulated further collaboration amongst our departments across the University of Pennsylvania (UPENN). Our MRI data set is of considerable interest to our radiology colleagues given our patients were scanned on a single unit without deviation. With this premise in mind, we are currently collaborating with radiology and neurosurgery to establish if there is plasticity in the brain following radiation. This project has been approved for an innovation grant funding within UPENN and we will work on institutional review board acceptance to use our MRI dataset for this purpose. The addition of our clinical and neurocognitive data will only add to the model that will be determined. This project has also been an educational project to medical and physics students who have lent their tireless energy in the early analysis of the data and want to continue to follow the project through to completion.

We are committed to providing complete analysis and conclusions at the completion of all time points and this dataset will likely lead to further research efforts in the use of protons and its effect in the brain.

Initial	Sex	Age	Study ID	Consent	EOT	Baseline	#1 ~1.5M	#2 ~6 M	#3 ~12 M	#4 ~24 M	Comments
				2011 / 2 females							
SXG	F	37	C2-001	9/14/2011	11/25/2011	10/3/2011	1/26/2012	4/5/2012	12/10/2012	1/13/2014	LGG
MXD	F	62	C2-002	10/11/2011	12/16/2011	11/2/2011	1/23/2012	6/4/2012	4/16/2012	12/16/2013	LGG
				2012 / 4 females, 2 males							
BXJ	F	48	C2-003	1/21/2012	3/13/2012	1/24/2012	4/17/2012	9/8/2012	5/3/2013	9/26/2014	BOS Meningioma
SBM	F	37	C2-004	5/16/2012	7/18/2012	6/4/2012	9/12/2012	1/28/2013	7/22/2013	8/4/2014	LGG
ALR	F	32	C1-001	6/19/2012	8/21/2012	7/3/2012	missed	4/19/2013	8/27/2013	8/25/2014	BOS-Schwannoma
SXM	M	31	C1-012	6/19/2012	9/12/2012	7/13/2012	missed	2/18/2013	9/16/2013	10/13/2014	BOS-Chondro
FAC	F	35	C1-011	6/20/2012	8/21/2012	7/3/2012	11/15/201	2/7/2013	7/29/2013	7/22/2014	BOS-Pituitary
ORO	M	27	C1-013	9/17/2012	11/5/2012	9/19/2012	2/25/2013	5/20/2013	9/13/2013	2/9/2015	BOS-Chordoma
				2013 / 6 females, 2 males							
SXZ	F	46	C1-002	2/8/2013	3/25/2013	2/8/2013	4/22/2013	9/17/2013	5/19/2014	3/20/2015	BOS-Pituitary
AXG	M	21	C1-014	2/15/2013	4/15/2013	2/28/2013	5/14/2013	10/18/2013	5/20/2014	5/20/15MRI 5/21/15Test	BOS-Pituitary
RXW	F	57	C1-015	4/11/2013	6/20/2013	4/23/2013	7/23/2013	12/12/2013	6/17/2014	7/6/2015	BOS-Chondro
NXP	F	28	C2-005	5/29/2013	8/5/2013	6/18/2013	9/19/13 tes 10/3/13 MRI	missed	8/6/2014		Meningioma
JAC	F	55	C1-016	8/15/2013	9/26/2013	8/15/2013	11/14/13te 11/15/13MRI	3/21/2014	10/6/2014		BOS-Schwan
				2013 cont							
KXS	F	32	C2-006	11/20/2013	1/28/2014	12/3/2013	3/24/2014	MISSED	2/16/2015		LGG

KXV	M	27	C2-007	12/4/2013	2/25/2014	1/10/2014	WITHDRAWN			LGG
LXF	F	35	C1-017	12/18/2013	3/3/2014	1/6/14test 1/20/14MRI	5/30/2014	MISSED		BOS-Meningioma
				2014 / 10 females, 3 males						
PXM	M	26	C2-008	1/29/2014	4/14/2014	2/24/2014	6/3/2014	10/14/2014		Meningioma
LXP	F	48	C2-009	3/5/2014	5/5/2014	3/19/2014	6/24/2014	MISSED	MISSED	LGG
EPM	F	55	C1-018	3/10/2014	4/28/2014	3/10/2014	6/9/2014	12/1/2014	4/8/2015	BOS-LGG
MXH	F	46	C1-019	4/11/2014	5/29/2014	4/11/14MR 4/16/14test	7/28/2014	12/30/2014MR 1/9/2014Test	MISSED	BOS-Meningioma
RXJ	F	48	C1-020	4/15/2014	6/5/2014	4/15/2014	7/30/2014	1/13/2015	6/9/2015	BOS-Pituitary
AXH	M	54	C1-021	4/14/2014	5/22/2014	4/14/2014	8/27/2014	12/10/2014Tes 12/18/2014MRI	5/14/2015	BOS-Pituitary
CXB	F	39	C1-022	4/16/2014	6/16/2014	4/22/2014	7/29/2014	12/9/2014MRI 12/22/2014Test	6/9/2015	BOS-Meningioma
ERM	F	27	C1-23	7/2/2014	9/5/2014	7/16/2014	10/28/201	2/25/2015MRI 3/2/2015Test		BOS-Pituitary
KDW	F	26	C2-010	8/25/2014	10/22/2014	9/3/2014	11/26/201	5/19/2015		LGG
LXM	F	64	C1-24	10/13/2014	12/1/2014	10/13/201	1/12/2015	6/8/2015		
				2014 cont						
PMM	F	57	C1-25	11/4/2014	1/8/2015	11/12/201	2/9/2015	7/7/2015		
SXA	M	53	C1-26	12/18/2014	3/7/2015	1/5/2014	4/27/15MR 4/29/15Test	9/30/2015		
BXG	F	45	C1-027	1/28/2015		2/4/2015	6/19/2015Test 6/22/2015MRI			
				2015 / 2 females, 3 males						
RMR	M	73	C1 - 003	4/13/2015	6/18/2015	4/13/15Tes 4/16/15MRI	8/13/2015			
RRL	M	66	C1 - 028	5/20/2015	7/16/2015	5/20/2015				

TXA	F	29	C1 - 029	5/27/2015		8/12/2015	T:6/10/2015 M:6/12/2015
MXR	M	36	C1 - 030	6/18/2015		8/4/2015	6/18/2015
SXW	F	56	C2-011	7/14/2015			

FEDERAL FINANCIAL REPORT

(Follow form instructions)

1. Federal Agency and Organizational Element to Which Report is Submitted	2. Federal Grant or Other Identifying Number Assigned by Federal Agency (To report multiple grants, use FFR Attachment)	Page	of
Department of The Army	W81XWH-09-2-0174	1	1 pages

3. Recipient Organization (Name and complete address including Zip code)

University of Pennsylvania
3451 Walnut Street, Franklin Bldg. P-221
Philadelphia, PA 19104-6205

4a. DUNS Number	4b. EIN	5. Recipient Account Number or Identifying Number (To report multiple grants, use FFR Attachment)	6. Report Type	7. Basis of Accounting
04-225-0712	23-1352685	553642 (#10)	X Quarterly □ Semi-Annual □ Annual □ Final	X Cash □ Accrual

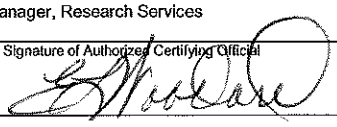
8. Project/Grant Period From: (Month, Day, Year)	To: (Month, Day, Year)	9. Reporting Period End Date (Month, Day, Year)
9/24/2009	9/30/2015	9/30/2015

10. Transactions	Cumulative
(Use lines a-c for single or multiple grant reporting)	
Federal Cash (To report multiple grants, also use FFR Attachment):	
a. Cash Receipts	$6,787,000.00
b. Cash Disbursements	$6,388,853.23
c. Cash on Hand (line a minus b)	$398,146.77
(Use lines d-o for single grant reporting)	
Federal Expenditures and Unobligated Balance:	
d. Total Federal funds authorized	$6,787,000.00
e. Federal share of expenditures	$6,388,853.23
f. Federal share of unliquidated obligations	$0.00
g. Total Federal share (sum of lines e and f)	$6,388,853.23
h. Unobligated balance of Federal funds (line d minus g)	$398,146.77
Recipient Share:	
i. Total recipient share required	$0.00
j. Recipient share of expenditures	$0.00
k. Remaining recipient share to be provided (line i minus j)	$0.00
Program Income:	
l. Total Federal program income earned	
m. Program income expended in accordance with the deduction alternative	
n. Program income expended in accordance with the addition alternative	
o. Unexpended program income (line l minus line m or line n)	

	a. Type	b. Rate	c. Period From	Period To	d. Base	e. Amount Charged	f. Federal Share
11. Indirect	Predetermined	59.90%	9/24/2009	6/30/2010	$ 185,296.80	$ 110,992.78	$ 110,992.78
Expense		60.00%	7/1/2010	9/30/2015	$ 1,928,343.32	$ 1,157,005.99	$ 1,157,005.99
				g. Totals:	$ 2,113,640.12	$ 1,267,998.78	$ 1,267,998.78

12. *Remarks: Attach any explanations deemed necessary or information required by Federal sponsoring agency in compliance with governing legislation:*

13. Certification: By signing this report, I certify that it is true, complete, and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent information may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

a. Typed or Printed Name and Title of Authorized Certifying Official	c. Telephone (Area code, number and extension)
Elvina Woodard Manager, Research Services	215-898-3148 d. Email address elvina@upenn.edu
b. Signature of Authorized Certifying Official	e. Date Report Submitted (Month, Day, Year)
	10/7/15
	14. Agency use only:

Standard Form 425
OMB Approval Number: 0348-0061
Expiration Date: 10/31/2011

QUARTERLY REPORT FORMAT - Fund # 553642 (#10)

1. Award No. W81XWH-09-2-0174 2. Report Date 10/6/2015

3. Reporting period from July 1, 2015 to September 30, 2015

4. PI Zelig A. Tochner 5. Telephone No. 215-662-6934

6. Institution The University of Pennsylvania

7. Project Title: "Proton Therapy Dose Characterization and Verification"

8. Current Staff, with percent effort on project.

Tochner, Zelig	13 %	Feriozzi, Ashley	67 %
Hill-Kayser, Christine	13 %	Zhu, Timothy	6 %
Finlay, Jarod	13 %	Sheng, Huang	100 %
Alonso-Basanta, Michelle	5 %	Gabriel, Peter	25 %
Doucette, Abigail Grace	70 %		

9. Award expenditures to date (as applicable):

	This Qtr/Cumulative		This Qtr/Cumulative	
Personnel	65,323.01 /	1,215,817.64	Travel	- / 20,966.15
Fringe Benefits	17,141.90 /	353,791.65	Equipment	60,769.03 / 2,179,228.68
Supplies	2,058.30 /	27,891.48	Other	30,287.63 / 1,323,158.83

	This Qtr/Cumulative	
Subtotal	$175,579.87 /	$5,120,854.43
Indirect Costs	52,499.67 /	1,267,998.80
Fee	$0.00 /	$0.00
Total	$228,079.54 /	$6,388,853.23

10. Comments on administrative and logistical matters.

11. Use additional page(s), as necessary to describe scientific progress for the quarter in terms of the tasks or objectives listed in the statement of work for this assistance agreement.

12. Use additional page(s) to present a brief statement of plans or milestones for the next quarter.

10/7/15

Elvina Woodard
Assistant Director