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| 14. ABSTRACT <p>This report describes continued work on the award "Neurocognitive Effects of Radiotherapy", which examines the neurocognitive and imaging impact of proton therapy for patients with low grade glioma and base of skull meningioma. A total of 48 patients have been enrolled, 18 of whom have enrolled in 2014. 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. Eight patients have completed neurocognitive and imaging evaluation at all planned timepoints, 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.</p> <p>A component (10%) of this award supports the Walter Reed Army Medical Center scientists (Appendix III). 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</p> | | |

15. SUBJECT TERMS

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

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Table of Contents

| | |
|--|-----------|
| Introduction | 7 |
| Body | 8 |
| Appendix I (Summary of Preliminary Data – Neurocognitive and Imaging) | 10 |
| Appendix II (Neurocognitive protocol) | |
| Appendix III (Walter Reed 2014 Summary) | |

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.

Progress

1. The first year's effort was dedicated to constructing an approved protocol to be used to study patients via MRI and neurocognitive testing. After revision for scientific and operational clarity, the protocol was approved by the Institutional Review Boards of both Penn and the DOD. Additionally, immobilization equipment that enables us to deliver base-of-skull treatments optimally was developed.
2. Having completed these tasks, we initiated patient recruitment in September, 2011.
3. 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 48 patients are now enrolled, with 18 having enrolled in 2014.
4. The majority of patients have completed baseline and 2 additional timepoints of neurocognitive testing and MRI, although the data are not mature enough to allow definitive analysis. Eight patients have completed evaluation at all planned testing timepoints as of October 2014. Preliminary neurocognitive analysis has been performed for the entire group, with extensive individual analysis presented as well.
5. MRI analysis continues separately from neurocognitive analysis, with recent identification of tools that exist within our department and that will allow further dosimetric correlation.
6. Michelle Alonso-Basanta continues to serve as Principle Investigator.

Appendix I. Summary of Preliminary Data – Neurocognitive and Imaging

2014 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 10/13/2014. We reviewed all enrolled patients to be sure they were in the appropriate cohorts. A total of 48 patients have been enrolled; 22 normal cohorts and 26 patients for cohorts 1 and 2.

The table attached includes all study procedures that have been completed as of 10/13/14. The most recent patient has only just consented on 10/13/14. Dates at each timepoint (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). Dr. Harish Poptani and Manoj Kumar have been overseeing every MRI obtained at each timepoint.

We have met with our statistician and have agreed upon initial formatting for data acquisition. We have included a very preliminary evaluation of the first 8 patients that have completed all timepoints. We will continue to meet every 2 months (as of August 2014) to provide updates on the current data and begin to provide some early conclusions.

Here are a few examples of what we have been doing and will be ongoing in the next year. We are attempting to summarize each patient’s clinical history, neurocognitive pattern and MRI results. These will then be summarized by cohorts and compared to each other as well as to historical controls (photon radiation) and normal controls (no radiation).

Clinical Update:

| 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 | | 64 Gy (50.4-79.2) | 54 Gy (54) |
| Laterality | | | |
| | Midline | 3 | 2 |
| | Right | 0 | 1 |
| | Left | 1 | 1 |
| Local Control | | 100% | 100% |
| Overall Survival | | 100% | 100% |

More detailed information has been acquired for each case. The above table will be expanded with further information on brain location, organs at risk and followed for toxicity. One example for a patient is detailed below. This information will then be analyzed compared to the patient's neurocognitive testing as well as MRI findings.

Example of Toxicity Summary for One Patient, Cohort 2.

- Cognitive disturbance: The patient had mild memory issues prior to surgery. Physician note says her memory improved at each visit, but the nursing ROS indicates progression- corresponds to her increase in Levetiracetam which the patient said causes her to be "scattered" (--> Increase of cognitive disturbance possibly secondary to medication)
- Headache: The patient was on eletriptan hydrobromide and rizatriptan benzoate for headaches since baseline. From 1.5-6months the patient did not report headaches. She had mild headaches at 12 months and moderate headaches at 24 months which the patient attributed to stress. (--> Increase in headache symptoms potentially due to stress trigger)
- Vision Changes: The patient seemed to have developed bilateral blurry vision mostly at night and when fatigued (--> Progressive mild vision decline that started at 6 months)
- Hearing changes: The patient developed mild right-sided hearing loss at 1.5 months after treatment. It progressed at 6 months and 12 months and was stable at 24 months. The radiation target was on the left side. (--> Development and progression of right-sided hearing loss with left sided radiation).
- Dysphasia: The patient had dysphasia at baseline. She worked with speech therapy and the dysphasia stabilized. Then it progressed at 24 months (--> Progressive mild to moderate dysphasia)

- Weakness: The patient had weakness at baseline that improved after treatment. (--> Mild weakness improved over time)
- Paresthesia: The patient had mild bilateral upper extremity paresthesias that improved with increasing doses of gabapentin. It was thought to possibly be due to seizure activity. (--> Developed paresthesia after treatment)
- Depression: The patient started with mild depression and was on three SSRIs over 24 months. Her depression progressed at 12 months and was stable at 24 months. (--> Depression continued and progressed at 12 months after RT and then stabilized. Present at time of radiation)
- Alopecia: The patient developed moderate alopecia that was evident at 1.5 months that improved by 6 months. Her alopecia resolved by 12 months. (--> Transient alopecia that resolved at 12 months)

Neurocognitive Testing: Preliminary Results (10/2014)

Proton versus Photon Patients Performance on Tests Confirmed for Sensitivity to RT

On the measures of verbal retrieval from long-term memory, the photon RT specific effect, initial data suggest that the patients treated with Proton RT also showed a post-treatment decline, but a stronger recovery over two years, with overall stronger memory capacity. These differences between groups were on the two tests most sensitive [retrieval after interference ($P=0.008$) and retrieval after time ($P=0.000$)]. This data must be further screened, and tumor location be taken into account.

Cerebellar Tests of Implicit Cognition

Proton patient's scores on the experimental cerebellar tests were compared at two time points in 20 patients with those of 20 screened healthy controls. Confirmatory evidence indicates that a decline in cognition occurs at the 1.5 months post treatment in standard of care, photon radiotherapy (RT). We wished to examine whether the cerebellar specific tests might be sensitive to proton RT, and compared them with controls who had also been tested twice, at the same 3 month interval (patients treatment 1.5 m + post treatment interval 1.5 m = 3 m). Several indices from five cerebellar specific tests were examined for the overall differences between patients and controls.

Some examples:

Timing Functions Test: A difference in the scores at the two time points was found for the test of perception of timing functions ($P=0.01$), with controls performing better than patients in estimating whether a time interval was faster or slower than a standard.

Serial Response Test: Reaction time was slower for patients than controls, with more patients demonstrating lower rates of implicit learning ($P<0.009$).

Audiovisual attentional shift test: Differences were not found between groups or over time in this test, except at the longest interstimulus intervals (ISI), suggesting a possible cerebellar effect from greater difficulty in estimating the target at longer time intervals. The effect of greater error at longer ISI was observed only for the auditory-only targets, and the condition of switching back and forth from cued auditory or visual targets. The effect was not found for visual-only targets. This demonstrates some greater vulnerability for estimating when targets have occurred for auditory inputs.

Summary:

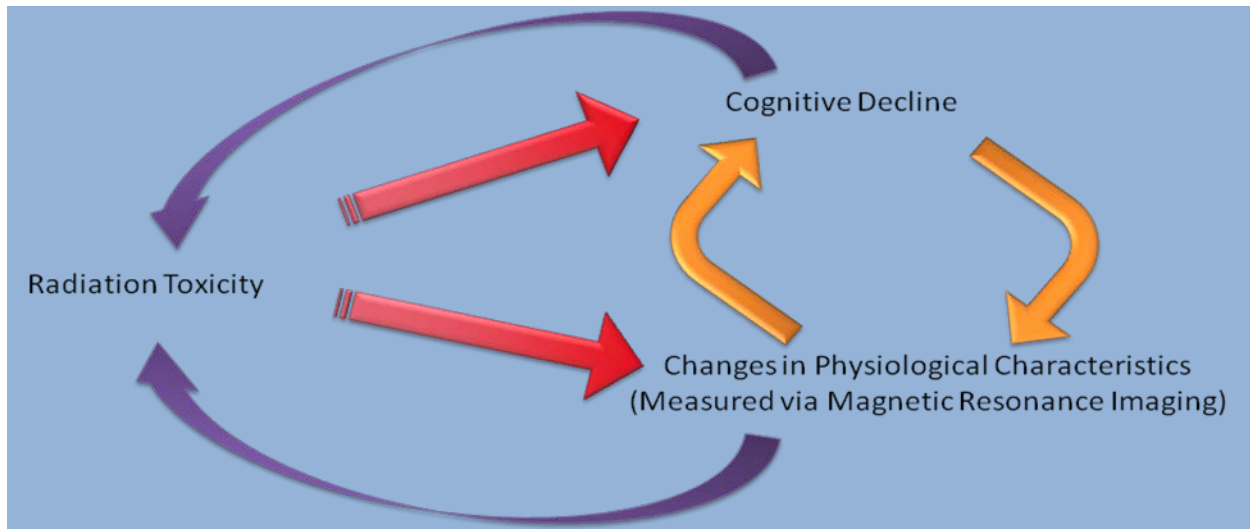
The cerebellar-specific, implicit cognition tests of Timing Functions, Serial Response Test, and Audiovisual attentional shift test with auditory stimuli showed promise for their use to measure effects of proton therapy on cognition.

MRI Evaluation: Update (10/2014)

MRI evaluation also began at this time and was independent of neurocognitive and clinical data so as to not bias any changes noted from baseline.

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 1).

Figure 1



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.

In our preliminary analysis from 2013, we reviewed the changes noted in the hippocampus bilaterally. Figure 2a shows the ADC for 12 patients at various time-points. Of note, there is limited data on many of these patients as they may have had only 1 or 2 time-points done in addition to baseline. Time 0 is baseline testing (pre-radiation) with each timepoint thereafter describing the time-points of the study (e.g. time 1=1.5 mo from completion of radiation, time 2=6 mo from completion, etc). Figure 2a shows the changes from baseline of the right hippocampus, Figure 2b shows the changes from baseline of the left hippocampus.

Figure 2a

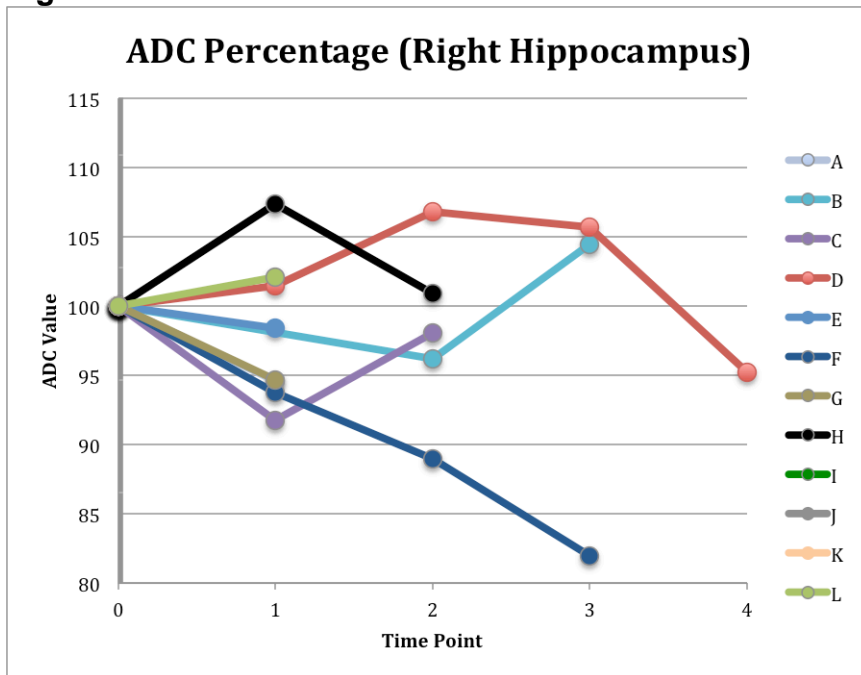
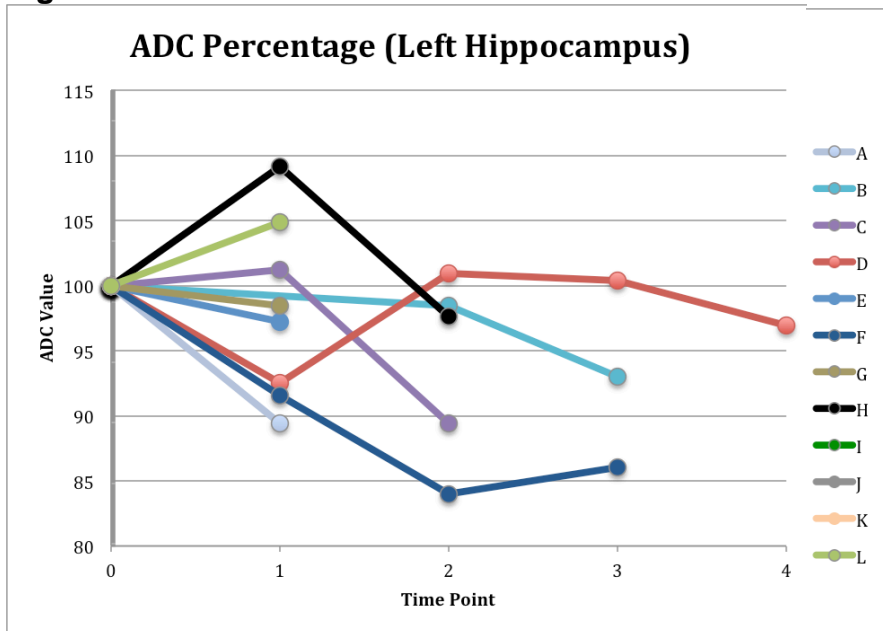
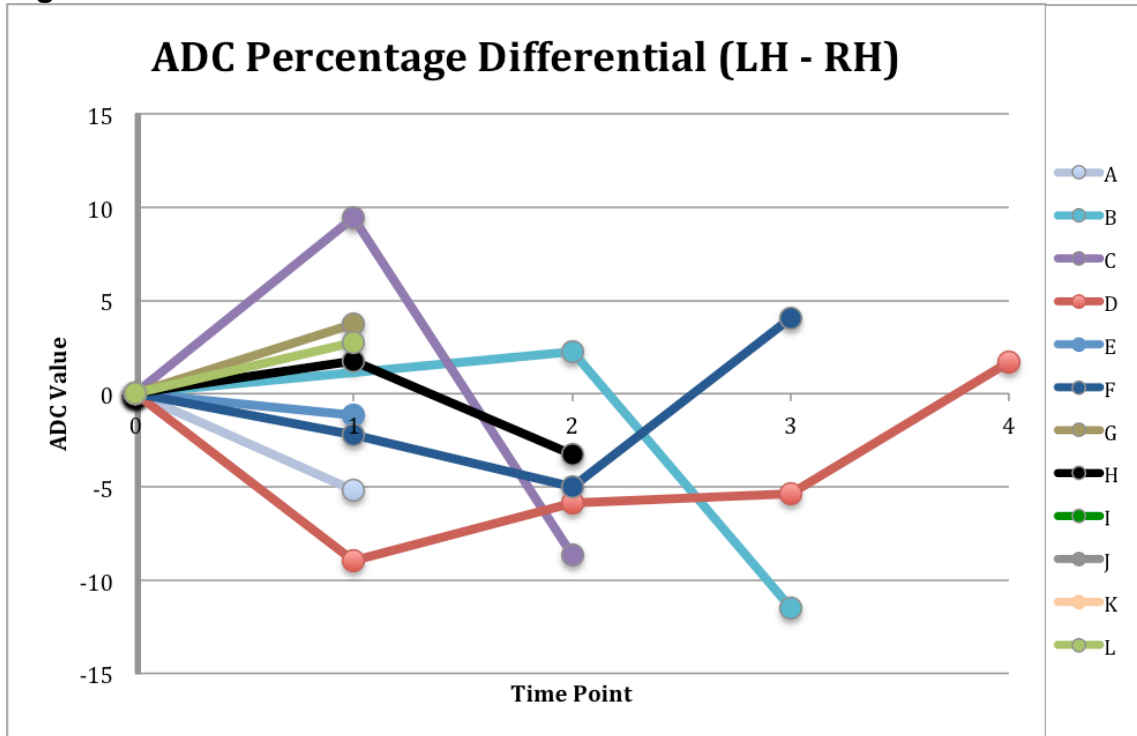


Figure 2b



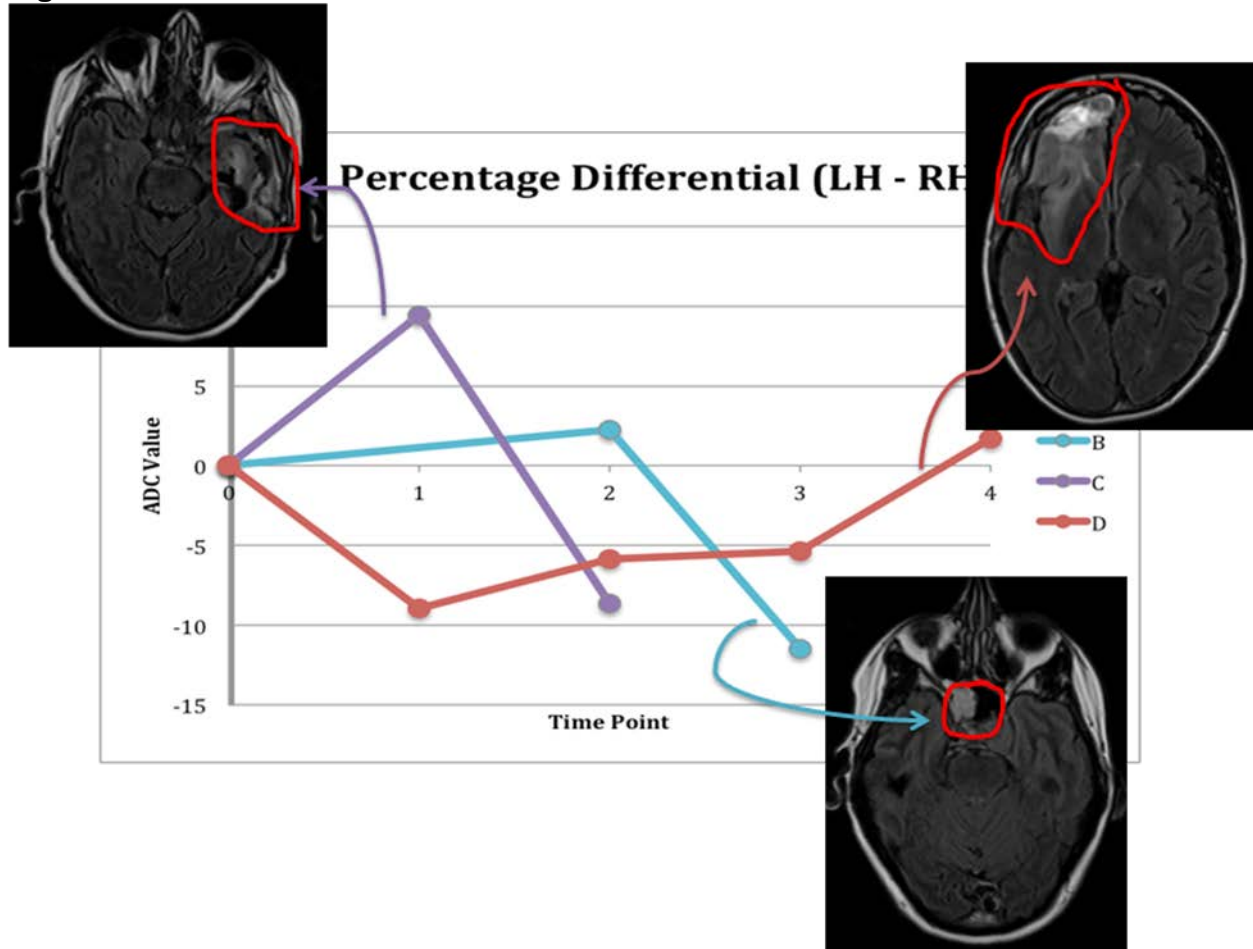
As can be seen, there are a number of patients with changes noted in ADC with patient E having a change and recovery in the left hippocampus but persistent change in the right hippocampus. When we review the differential difference (Figure 3), patients B through E have significant changes noted.

Figure 3



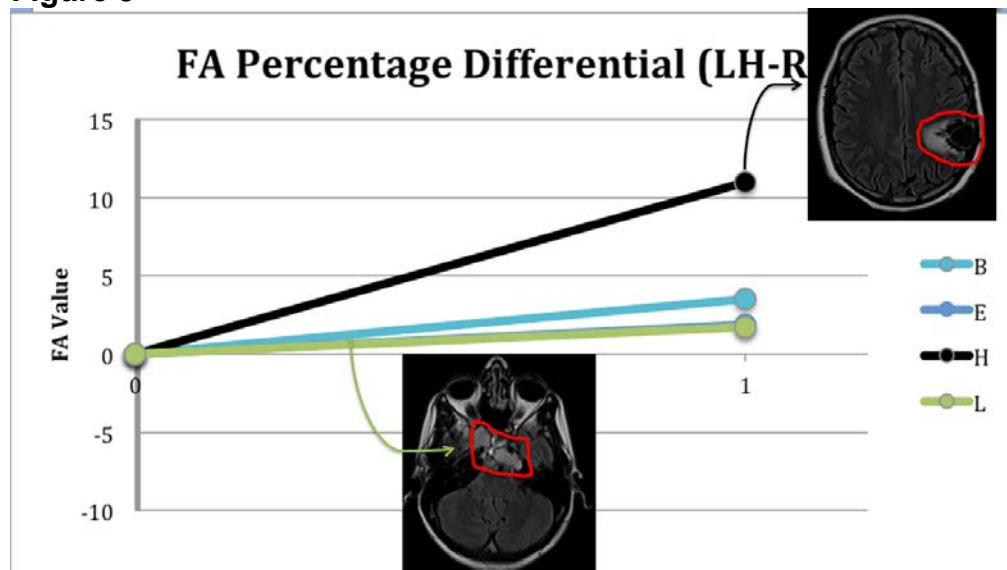
We therefore further reviewed the findings of three patients and correlated location of tumor to changes noted on ADC (Figure 4). On preliminary review, the changes noted correlate well with location of tumor as left sided tumors show preservation of the right hippocampus and left sided tumors show preservation of function on the left hippocampus. We will need to next correlate these changes with any neurocognitive changes in the patient and this analysis is currently ongoing.

Figure 4



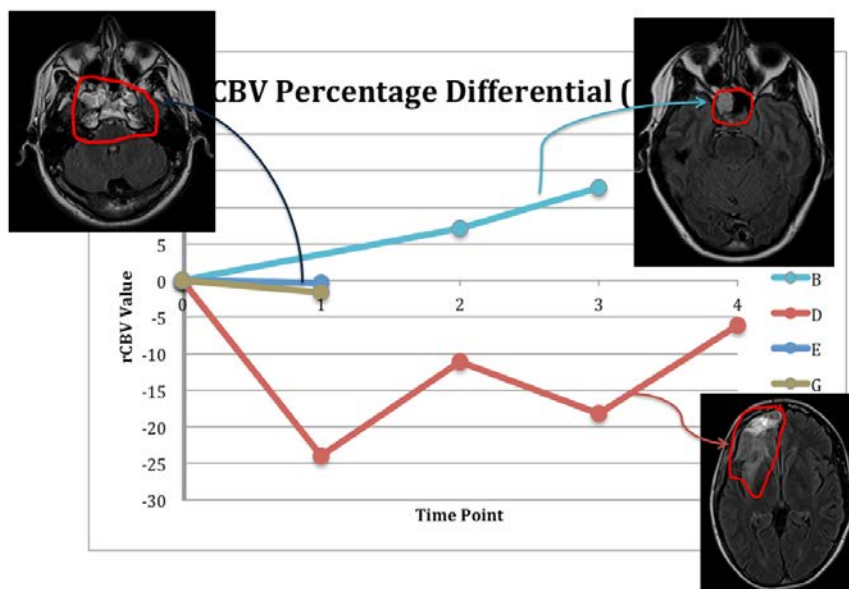
We then reviewed the FA value differential for these patients (Figure 5). The data is quite preliminary but suggests, as hypothesized, that skull base tumors – usually midline tumors – will have no difference in FA in the hippocampus however tumors in the brain parenchyma, with laterality, will have a change or direction (FA) noted between the left and right hippocampus.

Figure 5



We have also reviewed the rCBV value differential for these patients (Figure 6). This is very preliminary data but again notes a change in blood perfusion between the left and right hippocampus based on location. It suggests that midline bilateral tumors have no difference in rCBV in the bilateral hippocampus however tumors in the brain parenchyma or BOS tumors with laterality, will have a change rCBV noted between the left and right hippocampus.

Figure 6



In 2014, most of the data analysis has been on the neurocognitive portion. However, we have established there are programs (within the department and that should not add cost or effort to our current plan – i.e. Velocity ® or Mimvista ®) that will help facilitate the MRI interpretation and correlate these with dose. We are in the process of obtaining some assistance to do this so that we will have updated MRI data interpretation by our next quarterly analysis.

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 timepoints, we hope this will add to our early analysis. In addition, we will incorporate the MRI data to best determine early changes and evaluate correlations. We intend to submit an early publication of the data of the first few patients in early 2015.

Appendix II. Protocol



CLINICAL RESEARCH
PROTOCOL

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

SPONSOR: This study is being funded by a grant from the Department of Defense (DOD) Telemedicine and Advanced Technology Research Center (TATRC)

Protocol Number: IRB #811792; UPCC #08310

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Table of Contents

Study Summary/Abstract

- 1 Introduction
- 2 Study Objectives
- 3 Study Design
- 4 Subject Selection and Withdrawal
- 5 Study Procedures
- 6 Statistical Plan
- 7 Safety and Adverse Events
- 8 Data Handling and Record Keeping
- 9 Study Monitoring, Auditing, and Inspecting
- 10 Ethical Considerations
- 11 Study Finances
- 12 Publication Plan
- 13 References
- 14 Attachments

List of Abbreviations

| | |
|---------|---|
| RT | radiation therapy |
| cGy | centigray |
| IMRT | intensity modulated radiotherapy |
| IMPT | intensity modulated proton therapy |
| MRI | magnetic resonance imaging |
| fMRI | functional magnetic resonance imaging |
| ROI | region of interest |
| fROI | functional region of interest |
| NAA | N-acetyl aspartate |
| Cho | choline |
| Cr | creatine |
| rCBV | relative cerebral blood volume |
| rCBF | relative cerebral blood flow |
| FA | functional anisotropy |
| ADC | apparent diffusivity coefficient |
| MD | mean diffusivity |
| MNI | Montreal Neurological Institute |
| PI | Principal Investigator |
| AE | Adverse Event |
| SAE | Serious Adverse Event |
| GI | Gastrointestinal |
| IRB | Institutional Review Board |
| USAMRMC | US Army Medical Research and Material Command |
| ORP | Office of Research Protection |
| HRPO | Human Research Protection Office |

Study Summary

| | |
|---------------------------------------|---|
| Title | Detection of Vascular and Neuronal Changes Following Proton and/or Photon Radiotherapy in Patients Receiving Skull Base and/or Brain Radiation |
| Short Title | Skull base and Brain neurocognitive MRI study |
| Protocol Number | UPCC # 08310; IRB # 811792 |
| Phase | Not applicable |
| Methodology | Prospective, 2 cohorts, non-randomized |
| Study Duration | 3 years active enrollment |
| Study Center(s) | Single-center |
| Objectives | Primary Objective: To estimate the degree of memory loss, if any, following radiotherapy to the base of skull or brain as measured by standard neurocognitive battery testing. To describe radiotherapy dose-related changes in vascular perfusion, in spectroscopic parameters of neuronal injury and changes in the degree and directionality of tissue water diffusivity (diffusion tensor imaging) as a measure of white matter axonal injury. To relate these imaging characteristics to the degree of memory loss. |
| Number of Subjects | 30 cohort 1; 40 cohort 2; 70 normal group |
| Diagnosis and Main Inclusion Criteria | For cohort 1: Eligible study subjects will include subjects with a histological diagnosis of a tumor (benign or malignant) of the base of skull necessitating irradiation to a minimum of 45 Gy, ECOG PS 0-1 with no evidence of metastatic disease and an estimated life expectancy of at least 1 year and who is able to provide informed consent. Subjects will undergo standard CT simulation and radiotherapy treatment planning. For cohort 2: Eligible study subjects will include patients with a histological diagnosis of low grade glioma or meningioma requiring radiotherapy. ECOG PS 0-1 with no evidence of metastatic disease and an estimated life expectancy of at least 1 year and who is able to provide informed consent. Subjects will undergo standard CT simulation and radiotherapy treatment planning. |
| Statistical Methodology | Graphical methods and descriptive statistics will be generated to understand data quality and characterize distributions of the outcomes. Pearson's correlation will be employed to assess correlation between imaging and neurocognitive measures taken at the same time points. Within-patient changes between pairs of time points will be tested by paired t test. Within-patient trends over time will be analyzed with linear mixed effects models. Trends over time will be compared between groups using linear mixed effects models, in which a time by group interaction term is included. |

Abstract: Preliminary data suggests 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 demonstrate evidence of radiation induced subclinical vascular and neuronal injury in adjacent brain regions receiving exit doses of radiation. **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.

Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

Background

Standard **photon** radiation when administered for skull base and brain will result in exit radiation to adjacent normal brain tissue. This is due to the physical nature of the photon radiation depositing its energy along its entire physical path-length. Modern computer-based radiation treatment planning seeks to limit the risk of brain injury by conforming the radiation such that the total cumulative doses of radiation that is allowed to exit into the adjacent brain is sufficiently low to limit the risk of brain injury. However, the dose limit that is typically used is for the risk of developing **brain necrosis**. In general, radiation doses less than 60 Gy to the brain have been considered to be safe for this risk. Recent investigations have demonstrated that neurocognitive injury without the presence of brain necrosis, or **subclinical injury**, is a risk with both brain^{1,2} and skull base radiation^{3,4} and that this may occur at lower radiation doses typically regarded as safe. The mechanism(s) for this type of injury is largely unknown and has not been well studied.

Proton radiotherapy is unique in that the dose deposited along its physical path-length can be modulated with the entire radiation dose deposited at a defined depth significantly reducing the dose of radiation to adjacent normal tissue distal to this peak of radiation, referred to as the **Bragg peak**. As such, it becomes relevant to characterize the nature and the extent of any subclinical brain injury arising from skull base and brain radiation. This research protocol seeks to apply advanced MRI imaging techniques to temporally characterize these changes in the brain and to correlate the observed changes to the radiation dose and to determine if these also correlate with clinical manifestations of neurocognitive injury. This protocol will prospectively enroll two groups of patients: 1) subjects with **skull base** tumors (benign or malignant) treated with current state of the art conformal photon radiation techniques using **intensity modulated radiation therapy** (IMRT) followed by the enrollment of subjects treated with protons as this is gradually introduced into clinical practice at the Roberts Proton Therapy Center at the University of Pennsylvania and 2) patients with low grade gliomas or meningiomas who receive proton radiotherapy.

Radiation Induced Brain Injury:

Parameters that exacerbate or moderate radiation injury are: (1) host factors of age, white matter risk, and genetic risk; (2) the temporal phase of the effects: acute, early-delayed, and late-delayed, (3) concurrent clinical factors, such as hypertension and diabetes, (4) the radio therapeutic technique (e.g., whole brain versus proton therapy), and (5) cellular radiosensitivity. There is accumulating evidence that several mechanisms account for brain injury caused by irradiation. Radiation alters the permeability of the blood brain barrier (bbb) via the vascular endothelial cells. Glial cells are also moderately sensitive resulting in disruption of neural myelination and of transmission of neuronal signals. Increases in microglia in the hippocampal microenvironment are part of an immunologic inflammatory process that is also thought to cause injury⁵. Decrease in neuronal progenitor cells has also been observed in the hippocampus, which is a structure critical for memory. Injury is continuous, dynamic, and interactive with other tissues, especially hypoxia/ischemia, and inflammation⁶.

Clinical radiation injury is considered to have three distinct phases. This study focuses on the early-delayed and late-delayed phases. The early-delayed phase is sub acute, occurs weeks to months after treatment is completed, and may be followed by recovery of functions. Late-Delayed effects are not reversible, occur years after radiotherapy is completed, are often devastating, and can involve diffuse effects on brain structure and functions. Longitudinal structural brain imaging has shown that the most common type of injury is comprised of diffuse and sometimes progressive changes in the white matter. While glial injury, demyelination, and necrosis may be confined to the white matter, both grey and white matter is affected by vascular changes. It is very difficult to predict the severity of radiation injury that can be expected, even when the total dose and dose burden is known

because of little known clinical factors that also influence the severity and timing of injury. Vascular injury and glial atrophy may occur at a later time point than demyelination. Therefore, there are many types of possible radiation injury, but white matter is most vulnerable ⁷.

Cognitive effects of photon radiation injury:

It is thought that the early-delayed phase of radiotherapy results in temporary damage to the semantic associative memory network supported by the neocortex ⁸. In a brain tumor group-controlled, prospective, longitudinal study, only two measures of semantic memory demonstrated a significant change over time in the RT-treated group, although a comprehensive neuropsychological battery of repeatable measures, heavily weighted with memory and attention measures, was given to all patients. The slope of change described a decline six weeks after completion of radiotherapy (early-delayed period) followed by a rebound. The two radiotherapy-related measures were the post-encoding retrieval from long-term memory of semantic material (meaningful words and meaningful and nameable pictures). Both these measures require widespread semantic networks for retrieval, and suggest that a mechanism of temporary damage to the neocortex as well as to the hippocampus might be responsible for the early-delayed injury from radiotherapy. There are no reports of the effects of proton radiotherapy on brain structure or on cognitive functions.

The late-delayed cognitive effects are more variable; symptoms are irreversible and probably progressive ⁹. The onset of changes have been retrospectively described several months to many years post treatment ^{10,11}. There are few prospective studies of the late-delayed time points in patients with nonmalignant disease. Studies of patients with low-grade brain tumors, whose disease causes less damage at baseline than malignant tumors, report much less significant damaging effects on cognition 2-4 years after treatment ^{7,12}. While retrospective reports and individual case studies demonstrate the severity that late-delayed damage from RT can cause, there is little information on the actual frequency of such severe damage. MRIs showed mildly increasing white matter hyper intensities and white matter atrophy over the first three years post treatment with unclear progression. The few cognitive studies that exist indicate radiation-specific injury that is progressive. Injury and progression appear to be specific to individuals who carry risk factors. In general, cognitive risks, as discriminated from progressive injury due to neoplastic malignancy, appear selective to memory ^{7,12,13}.

Some patients will receive radiotherapy to the cerebellum as part of their standard care. There are no extant studies of the neurocognitive effects from irradiation of the cerebellum.

Neuroimaging measurement of damage from photon radiotherapy:

A vascular mechanism for radiation induced subclinical brain injury was suggested by Price and colleagues who demonstrated a significant dose-related reduction in the relative blood volume and flow in adjacent normal brain regions in 4 subjects receiving conformal standard fractionated irradiation for low-grade gliomas at 3 months ¹⁴. MR dynamic contrast susceptibility perfusion imaging of predetermined anatomic regions of interest (ROI) in the white matter was correlated with the summarized radiotherapy doses to these ROIs. No significant changes in blood flow (rCBF) or volume (rCBV) was seen in regions receiving less than 32 Gy with significant differences seen greater than 4 months and receiving more than 43 Gy. The rCBF and rCBV were normalized to the baseline studies. At 42 days, imaging demonstrated that the rCBF and rCBV tended to be higher with higher radiation doses (> 43 Gy) and at 132 days, consistently lower in white matter regions receiving higher radiation doses. No neurocognitive testing was performed.

Direct subclinical evidence of neuronal injury which may or may not be independent of vascular injury has also been demonstrated with radiation to the brain as characterized by the use of MRI proton spectroscopy ¹⁵⁻¹⁷. The long-term clinical significance of these changes is unclear at this time. Sundgren and colleagues reported the results of a prospective study of 11 subjects with low grade or benign tumors imaged serially with a 2D multivoxel MR spectroscopic technique out to 6 months ¹⁵. All patients were treated 1.8 Gy daily, Monday to Friday, for 28-33 fractions, resulting in 50.4-59.4 Gy to the tumor. Signs of occult neuronal injury were seen as early as 3 weeks during a course of radiotherapy as demonstrated by significant decreases in the NAA/Cr and Cho/Cr ratios. These metabolites remained significantly decreased out to 6 months. The metabolite NAA (N-acetyl-aspartate) is believed to represent a marker of neuronal density and function and its progressive reduction over time (especially at 6 months) suggests that the process of neuronal damage continued long after the completion of RT. Choline is a

marker of cell membrane biosynthesis and its metabolic turnover and is felt to reflect glial cell proliferation. There was no correlation with the dose delivered when analyzed at 6 months except for a relationship between the decreases in the Cho/Cr ratio up to 1 month from completion of the radiotherapy and larger volumes of normal brain receiving higher doses (>40 Gy).

Collectively, these limited studies are provocative in suggesting that modern advanced imaging techniques that assess the function of the brain offer the potential to better understand the mechanism of subclinical radiation-induced changes to the brain. Subclinical neuronal damage can be detected but it is unclear if these are separate of any vascular injury. The risk of vascular injury may be dose-related and possibly more likely to be a dominant mechanism of injury at higher radiation doses. The inter-relationship between the risk of neuronal injury, vascular changes and radiation dose has not been well studied and is important to characterize to determine to what extent the application of proton radiotherapy treatment planning may help to reduce this risk.

Low Grade Gliomas:

There are approximately 8,000 new low grade gliomas (LGG) diagnosed each year in the United States **Central Brain Tumor Registry of the United States (CBTRUS)**¹⁸. These include astrocytomas, oligodendrogliomas and mixed tumors. There is no consensus as to the appropriate treatment for these tumors. Treatments include surgery, biopsy or resection, radiation, and chemotherapy, or a combination of these treatments. In the era of enhanced imaging technologies, some physicians have advocated for early intervention with surgery, radiotherapy and/or chemotherapy; however, the optimal timing and sequencing of these therapies remains unclear.

There are two main issues in the management of LGGs with respect to radiotherapy: timing (at diagnosis vs. at progression) and appropriate radiation dose. There are 3 randomized trials on the use of radiation for the treatment of LGG. Shaw et al¹⁹ reported on the results of Radiation Therapy Oncology Group (RTOG) 8602, which was a randomized study of high dose (64.8 Gy/36 fractions) vs. low dose (50.4 Gy/28 fractions) radiotherapy immediately following resection in patients with LGG. This study included 203 patients treated from 1986 to 1994. Survival at 2 and 5 years was non-significantly better in the low dose group (72% v 64%, respectively). The European Organization for Research and Treatment of Cancer (EORTC) trial 22844, Karim et al²⁰, reported on 379 adults with LGG randomized to either 45Gy or 59.4Gy in 1.8Gy fractions. They found no difference in overall survival for patients receiving low dose vs. high dose radiotherapy, 58% vs. 59%, respectively or in progression free survival 47% v 50%, respectively. The minimum follow up was 50 months with a median of 74 months. Early versus delayed post operative radiation was explored in (EORTC) 22845²¹. Following surgery, patients were randomized to either immediate radiation therapy to 54Gy or delayed radiation of the same dose delivered at the time of progression. Three hundred and fourteen patients were randomized. Progression free survival was 5.3 years in the early radiation group versus 3.4 years in the delayed group. Median survival was 7.4 years in the early group and 7.2 years in the delayed group. In the delayed group 65% of the patients received radiation at the time of progression. It was also noted that at one year seizures were better controlled in the early radiation group.

Prognostic factors for patients with LGG were analyzed by Pignatti et al²². They reviewed patients with LGG treated in EORTC studies 22844 and 22845. Relevant factors include age greater or less than 40, tumor size, greater or less than 6cm, tumor crossing the midline, histological subtype, and pre-surgery neurologic deficit to be determinants of outcome. Chang et al²³ reported on a group of 281 adult patients with LGG treated at the University of California at San Francisco. They developed a preoperative prognostic scoring system using age greater than 50, Karnofsky Performance Status (KPS) 80 or less, tumor location in an eloquent area, or a tumor over 4cm. Based on their system 3 separate groups could be identified.

The role of chemotherapy for patients with LGG is still uncertain. RTOG 9802 randomized high risk LGG patients following surgery to either radiation to 54Gy or to radiation followed by 6 cycles of Procarbazine, Lomustine, and Vincristine (PCV). The early reports show an improvement in progression free survival for induction chemotherapy but no improvement in overall survival.²⁴ There is no clear consensus at this time exactly what role chemotherapy should play in the treatment of newly diagnosed LGG.

Kiebert et al²⁵ reported on quality of life (QOL) post radiation in EORTC study 22844. This was a secondary non-mandatory end point. Only 180 of 379 randomized patients completed at least one QOL form. This study only reported data on the initial, 3, 6, and 12 month time points as there were too few forms filled out at later time points. In general, patients receiving the high dose radiation reported lower functioning levels and higher

symptom burdens. The groups were significantly different for fatigue and insomnia immediately post therapy with approximately 40% reporting severe fatigue in the lower dose arm and 55% in the higher dose arm. A difference in leisure time and emotional functioning at 7-12 months also favored the lower dose arm. Klein et al¹³ attempted to evaluate the effect of radiation and other treatment factors on long term cognitive outcomes in LGG patients. The study compared 195 LGG patients, 104 of whom had received radiation, to 100 patients with low grade hematological malignancies. LGG patients had lower ability in all cognitive areas compared to low grade hematological patients and the disparity was even worse when the LGG patients were compared to healthy controls. Cognitive disability in the memory domain was found only in radiation patients treated with fractions greater than 2Gy. The use of antiepileptic drugs was strongly associated with impairment in attentional and executive function. However, Surma-aho et al²⁶ reported on patients with LGG who had either surgery only or surgery followed by radiation. The group who received radiation demonstrated poorer cognitive function and lower KPSs. There is no prospective quality of life data or prospective neurocognitive studies on patients with LGG treated with proton beam radiation. There are also no prospective studies on the incidence and severity of fatigue in this group of patients.

The Kibert²⁵ study showed a dose response in 2 domains of QOL. Therefore, the ability of proton beam radiation to deliver an extremely conformal dose to the tumor while allowing very significant sparing of normal tissue should allow for similar local control rates as photon beams but with improved neurocognitive outcome and better QOL. The significant reduction of the integral dose of radiation to the brain may also lessen the incidence and degree of fatigue reported in patients with brain tumors treated by radiation therapy.

Potential Impact of Proton Radiotherapy Treatment Planning:

Of the two published studies that have examined the impact of skull base radiation on neurocognition, one series studied the impact of proton irradiation for chordomas and low-grade chondrosarcoma and were prospectively evaluated with baseline and follow-up neurocognitive evaluations⁴. The median prescribed tumor dose was 68.4 CGE. The other represented a retrospective report of the impact of traditional photon treatment planning for carcinomas of the paranasal sinus with post-treatment neurocognitive evaluation delivering more than 60 Gy³. In the group treated with proton irradiation at the skull base, no significant changes in various neurocognitive domains were seen with the last evaluation at approximately 7 months from the end of treatment⁴. In contrast, in the group receiving 60-70 Gy for paranasal sinus carcinomas, patient performance was significantly below that expected with tests of memory function³. There is a suggestion that in part, the difference in neurocognition may have been related to the mean dose delivered to the hippocampus with the group receiving protons having a maximum dose ranging between 34 to 44 Gy compared to >60 Gy in the group with neurocognitive deficits.

Summary:

Subclinical neuronal and vascular changes in adjacent normal brain tissue receiving exit radiation can be identified with the application of serial advanced imaging techniques especially with MRI techniques that offer the ability for multi-parametric evaluation. The ability to draw more generalized conclusions from these studies is limited for several reasons including the small study populations, the lack of neurocognitive evaluation and the potential confounding effects of the tumor on the surrounding normal brain tissue under study.

As such, this project will evaluate a patient population with skull base tumors that will reduce the influence of tumor on the normal brain tissue whose prognosis will facilitate long-term follow-up evaluation. Additionally, we will evaluate a group of patients with low grade gliomas and meningiomas to understand what if any long-term cognitive decline can be mitigated with proton beam radiotherapy.

The interpretation of deficits found in neurocognitive testing as it relates to the radiation dose is fundamentally a clinically relevant research relationship which is limited by the anatomic localization of regions of the brain involved in specific neurocognitive tasks. As a secondary objective, we will apply MRI techniques to both characterize the underlying nature of the brain injury but also to help improve the localization of regions that may be involved in specific neurocognitive tasks.

We anticipate that as protons are gradually introduced into clinical practice and as the more conformal **intensity modulated proton therapy technique (IMPT)** is technically developed, we will be able to assess if protons may reduce the subclinical injury characterized with conformal photons such as IMRT.

Our proposed study will include three cohorts: 1) patients with tumors involving the skull base who may have incidental radiation dose to adjacent normal brain, and 2) patients with low grade glioma or meningioma receiving radiotherapy. 3) In addition, there will be a normal group of patients that will undergo neurocognitive testing at two timepoints for cerebellar comparison.

Risk/Benefits

NEURO-COGNITIVE TESTING RISKS: Neuro-cognitive testing can cause fatigue in some individuals. It is possible that a subject could have anxiety regarding test performance.

MRI RISKS:

The risks of magnetic resonance imaging studies are minimal. The levels of energy used to make magnetic resonance measurements are far less than are used in a single X-ray, and many people have been safely studied using magnetic resonance techniques. However, some people become uncomfortable or claustrophobic while inside the magnet. If the subject becomes uncomfortable inside the magnet, they may withdraw immediately from the study.

The greatest risk is a metallic object flying through the air toward the magnet and hitting the subject. To reduce this risk we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. No metal objects are allowed to be brought into the magnet room at any time. In addition, once the subject is in the magnet, the door to the room will be closed so that no one will accidentally walk into the magnet room.

During some of the MRI scans, subjects have occasionally reported temporary tingling or twitching sensations in their arms or legs, especially when their hands are clasped together. Because of the strong magnetic field, people with pacemakers, metal fragments in the eye, or certain metallic implants cannot participate in this study. The subject will be given a checklist before entering the MRI room, to obtain a history that the subject does not have a contraindication.

One part of the study may require injection of a contrast agent (or "dye") called gadolinium through a temporary IV in the hand or arm, and this is the same contrast agent used for routine clinical studies. The IV (intravenous) contrast agent is routinely given during clinical exams, and has been approved for that purpose for many years. The main risk is of a reaction to the IV contrast agent, and such a reaction is exceedingly rare. In light of recent reports of a possible risk of nephrogenic systemic fibrosis (NSF, also referred to as nephrogenic fibrosing dermopathy or NFD) occurring following administration of a Gadolinium-based contrast agent, subjects with known moderate to severe renal disease will be excluded from the research study. (See Attachment B for calculation method)

PREGNANCY RISKS:

Although there are no known risks of MRI to pregnant women or the fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is no direct benefit from participating in this protocol for a pregnant woman, pregnant women are not eligible to participate in this study. If the subject is a woman of child-bearing potential, a negative pregnancy test (urine) will be required before participation in this study.

ABNORMAL FINDINGS:

These studies are part of a research study and are not intended to provide a comprehensive clinical MRI examination of the brain. In the unlikely event that a significant brain abnormality is found while processing the subject's brain images for the research study, the subject will be contacted and we will arrange for an appropriate medical referral.

The benefits associated with the research project is limited to the advancement of knowledge about the risks and the nature of subclinical radiation induced brain injury and determining if this is clinically relevant in subjects with gliomas, meningiomas and skull base tumors (benign or malignant). There is no anticipated direct benefit to the study subject. In summary, the risks associated with the imaging studies are modestly greater than minimal risk with efforts established to minimize these risks. The risks associated with neurocognitive testing are minimal. The potential benefits with knowledge derived from the diagnostic interventions include the development of ways to apply protons to minimize the risk of functional neurocognitive injury. Insights gained will likely have relevance in the development of pharmaceutical radioprotectants. As such, this offers a favorable risk-benefit assessment for this research plan.

Study Objectives

Primary Objectives

To estimate the degree of cognitive loss, if any, following radiotherapy to the base of skull or brain as measured by standard neurocognitive battery testing using a prospective, longitudinal design beginning prior to radiotherapy (approximately baseline), and then approximately 1.5, 6, 12, and 24 months post completion of radiotherapy.

- 2.1.1 To determine the neurocognitive change in patients with tumors (benign or malignant) involving the base of skull who receive proton beam radiotherapy, as compared to a contemporary group of patients treated with photon beam radiotherapy.
- 2.1.2 To determine the neurocognitive change in patients receiving proton beam radiotherapy for low grade glioma or meningioma as compared to a historical group of patients who have received photon beam radiotherapy in the University of Pennsylvania Longitudinal Study of Radiation Effects on Cognition^{7,27} as measured by prospective, longitudinal neurocognitive testing.

Secondary Objectives

- 2.2.1 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.

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).

To correlate the MRI findings in regions of interest (ROIs) with neurocognitive changes, focusing initially on changes in memory.

Study Design

General Design

The study design will prospectively enroll study subjects to a research MRI/neurocognitive study with 2 cohorts, consisting of subjects who have skull base tumors (benign or malignant) and subjects who have low grade gliomas or meningiomas. Subjects will have MRI imaging and neurocognitive evaluation at approximately baseline, at the approximately 1.5, 6, 12 and 24 months after the completion of the radiotherapy. The table below outlines this schedule. The baseline studies will be coordinated to avoid delays in the start of the standard oncologic treatment.

| | Evaluation | Baseline | Approx 1.5 months from day of last RT tx | Approx 6 months from day of last RT tx | Approx 12 Months from day of last RT tx | Approx 24 months from day of last RT tx |
|---------------------------------------|----------------------|------------|--|--|---|---|
| Base of Skull (n=30) | Standard of Care MRI | X | X | X | X | X |
| | Advanced Imaging | X Research | X Research | X Research | X Research | X Research |
| | Neurocog testing | X Research | X Research | X Research | X Research | X Research |
| Low Grade Glioma or meningioma (n=40) | Standard MRI | X | X | X | X | X |
| | Advanced Imaging | X Research | X Research | X Research | X Research | X Research |
| | Neurocog testing | X Research | X Research | X Research | X Research | X Research |

* Visits will occur at time points based on time of baseline visit (approximately the three months for normal controls and approximately 1.5 months post treatment end date for treatment cohorts)

Standard Treatment

For patients with skull base tumors (benign or malignant) (cohort 1), treatment will consist of daily fractionated radiotherapy utilizing an IMRT technique at the time of initial study accrual. As experience with proton therapy increases its application will be introduced to the skull base at which time subjects treated with protons as a component of their treatment will be enrolled. The total dose prescription will be dependent on the clinical indications. This will reflect whether or not surgery was performed and the pathologic features necessitating post-operative irradiation. Study subjects may or may not receive concurrent chemotherapy depending on the clinical indications.

For patients with low grade gliomas or meningiomas (cohort 2), treatment will be with protons alone. Normal subjects will not receive radiotherapy.

Study Subject Enrollment

The study will enroll subjects to two cohorts.

| | Photon | Protons |
|------------------------------|--------|---------|
| Number of Subjects Cohort 1 | 10 | 20 |
| Number of Subjects Cohort 2: | | 40 |

The normal group will participate only in a portion of the neurocognitive testing, for a total n=70. The normal subject group will be matched in age and education with the cohort groups.

Research Imaging

MRI Protocol

Patients will have the following clinical MR imaging protocols on the Department of Radiation Oncology 1.5 Tesla MR Scanner. Imaging time will be 60-90 minutes in duration. An intravenous line will be placed to facilitate the administration of gadolinium. Standard MRI precautions will be undertaken to minimize risks typically associated with imaging in a 1.5T magnet.

Anatomic Imaging:

Standard structural imaging sequences, including axial 3D T1-weighted Magnetization Prepared Rapid Gradient Echo (MP-RAGE) pulse sequence before and after contrast, sagittal 3D T2-weighted, and axial Fluid Attenuated Inversion Recovery (FLAIR) pulse sequence.

Blood volume measurements:

Dynamic susceptibility contrast (DSC) PWI will be obtained during the first pass of a 12ml bolus of gadodiamide (Omniscan™) contrast agent followed a loading dose of 3ml gadodiamide (gradient echo EPI, GRAPPA with acceleration factor of 2, TR/TE 2000/45msec, slice thickness 3mm, voxel size 1.72x1.72x3mm³, 20 slices).

Diffusion Tensor Imaging:

DTI will be acquired with a 12-direction, single shot, spin-echo echo planar sequence. Imaging parameters were as follows: 6500/99, field of view (FOV) 22 x 22 cm², 3mm slice thickness, 128 x 128 matrix, b values = 0 and 1000 s/mm² and 40 slices covering the whole brain. The acquisition time for the DTI images was about 8 minutes.

DTI Image Processing:

Three eigenvalues and eigenvectors of diffusion tensors for each pixel were calculated using multivariate fitting with “DTI-Task-Card” (Version 1.69, MGH, Boston, MA). Subsequently, ADC and FA maps were calculated according to equations (1) and (2), respectively.

$$ADC = \left(\frac{\lambda_1 + \lambda_2 + \lambda_3}{3} \right) \quad (1)$$

$$FA = \sqrt{\frac{3}{2}} \sqrt{\frac{(\lambda_1 - \bar{\lambda})^2 + (\lambda_2 - \bar{\lambda})^2 + (\lambda_3 - \bar{\lambda})^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \quad (2)$$

MRS:

Single slice 2D multivoxel ¹H MRSI will be performed using a spin echo sequence with water suppression using a TR/TE = 1700/30ms, NEX = 3, field of view = 16x16 cm², BW=1200 Hz, matrix size = 16x16. The volume of interest (VOI) will be selected such that to include the enhancing region as well as peritumoral region of the neoplasm and contralateral normal parenchyma avoiding the scalp, skull base or sinuses. Eight outer volume saturation slabs (30mm thick) will be placed outside the VOI to suppress lipid signals from the scalp. Both water suppressed and unsuppressed ¹H MRSI spectra will be acquired and the unsuppressed water signal will be used for computing metabolite concentrations.

MRS Data Analysis

All ¹H MRS data will be analyzed using a user-independent spectral fit program [Linear Combination (LC) Model]. The region between 0.2 and 4.0 ppm of the spectrum will be analyzed and the following metabolites will be evaluated: N-acetyl aspartate (NAA) 2.02ppm; Cr, 3.02 ppm; Cho, 3.22 ppm; glutamate+glutamine (Glx), 2.24-2.34ppm; myo-inositol (mI), 3.56 ppm. The NAA/Cr, Cho/Cr and NAA/Cho ratios will be computed.

Neuropsychological Measurements

University of Pennsylvania Longitudinal Study Cognitive Battery:

Attention:

1. Audio-Visual Attention Shifting T. – speed and accuracy in shifting attention from auditory to visual to inputs²⁹;

Associative and Long-Term Memory:

3. Rey Auditory Verbal Learning T.,
4. Biber Figure Learning T.³⁰,
5. Picture Recognition T.³¹;
6. Hopkins Verbal Learning Test

Procedural Learning:

7. Serial Response Task – reaction time to learn an implicit sequence³²;
8. Semantic Fluency Test (Animals);

Executive and Conceptual Processes:

9. Balls in a Bottle Test – an inferential reasoning task³³,
10. Timing Functions T. – perception of time intervals³⁴;
11. Trails B
12. Phonemic Fluency Test

Visuomotor Scanning Speed:

13. Trails A

Mood, fatigue:

14. Fatigue Severity Scale³⁵,
15. Beck Depression Inventory,
16. Beck Anxiety Inventory.

Primary Study Endpoints

A priori hypotheses about memory will be tested in the mixed model as expected slopes of linear change over time.

Secondary Study Endpoints

Correlations with regional imaging measurements/quantitations will first be tested with domain composite scores. Individual hypotheses about association of cognition with radiation sensitive brain structures, such as the hippocampus and cerebellum, will exploit individual neurocognitive functions. For example, we expect a relationship, such as the relationship of associative memory to hippocampus quantitations, and serial response learning to cerebellar quantitations.

Blood volume measurements will be summarized by determining the rCBV (relative cerebral blood volume) and rCBF (relative cerebral blood flow).

Spectroscopy measurements will be summarized by the metabolic ratios NAA/Cr, Cho/Cr and NAA/Cho.

Diffusion tensor imaging will be summarized by the fractional anisotropy (FA). Diffusivity will be summarized by the apparent diffusivity coefficient (ADC), mean diffusivity (MD), parallel and perpendicular averaged water diffusivity.

Primary Safety Endpoints

There are no primary safety endpoints as this is not a therapeutic intervention study.

Subject Selection and Withdrawal

Inclusion Criteria for Cohort 1 (Patients with tumors (benign or malignant) involving the base of skull)

Study subjects capable of providing informed consent.

Study subjects with an ECOG performance status of 0-1 or KPS of 60-100.

Study subjects aged 18 or greater.

Study subjects with a histological diagnosis of a tumor (benign or malignant) of the base of skull requiring either definitive or post-operative radiation to a minimum prescribed dose of 45 Gy.

Study subjects deemed capable of undergoing standard CT simulation and radiotherapy treatment planning and delivery including the capacity to comply with standard immobilization devices to the head and neck for daily irradiation.

Study subjects without any evidence of distant metastasis.

Study subjects with an estimated life expectancy of at least 1 year.

Study subjects who are able to receive a standard MRI study and deemed capable of complying with the immobilization needs.

Female study subjects of reproductive potential with a negative pregnancy test prior to each scheduled MRI study.

Adequate bone marrow function and renal function: WBC greater than or equal to $4000/\text{mm}^3$, platelets greater than or equal to $100,000/\text{mm}^3$ and Creatinine clearance of greater than 45.

Inclusion Criteria for Cohort 2 (Patients with Low Grade Gliomas or meningiomas)

Patients must be able to provide informed consent.

4.2.2 Study subjects with an ECOG performance status of 0-1 or KPS of 60-100.

4.2.3 Age greater than or equal to 18.

4.2.4 Histological confirmed diagnosis of low grade glioma (WHO grade II) or meningioma (WHO grade I) of the CNS.

- 4.2.5 Subjects deemed capable of undergoing standard CT simulation and radiotherapy treatment planning and delivery including the capacity to comply with standard immobilization devices to the brain for daily irradiation.
- 4.2.6 Patients with no evidence of distant metastases.
- 4.2.7 Adequate bone marrow function and renal function: WBC greater than or equal to 4000/mm³, platelets greater than or equal to 100,000 mm³ and Creatine clearance of greater than 45.
- 4.2.8 Women of child-bearing potential as long as she agrees to use a recognized method of birth control (e.g. oral contraceptive, IUD, condoms or other barrier methods etc.). Hysterectomy or menopause must be clinically documented.

Exclusion Criteria for Both Cohorts

Study subjects with a Karnofsky performance status less than 60 or ECOG 2-4 whose life expectancy is less than 1 year.

Study subjects with anxiety that precludes the safe administration of a MRI for the imaging time required.

Study subjects with major documented psychiatric diagnosis prior to neuro-oncologic diagnosis.

For neuropsychological studies, study subjects with neurological or behavioral issues that would preclude compliance with study procedures.

Study subjects with an inability to undergo MR Imaging for any reason.

4.3.6 Study subjects with a history of renal transplant or known renal disorder with a calculated GFR > 45mL/1min [gadolinium restriction] (*SEE Attachment B FOR CALCULATION INFORMATION*)

4.3.7 Study subjects must be fluent in English.

4.3.8 Pregnant women, women planning to become pregnant and women who are nursing.

4.3.9 Prior or simultaneous malignancies within the past two years (other than cutaneous squamous or basal cell carcinoma, melanoma in situ or well differentiated thyroid carcinoma)

4.3.10 Additional Exclusion Criteria for Cohort 2 (Patients with Low Grade Gliomas or meningiomas)

4.3.10.1 Patients with the following histologies are excluded: gliomatosis cerebri, WHO III or IV gliomas

Subject Recruitment and Screening

Subjects will be recruited from the Oncology practices from either the Department of Defense oncology practices or by Penn Medical Center. Potential study subjects will also be identified from both weekly head and neck/brain tumor conferences and skull base tumor conferences held at the Hospital of the University of Pennsylvania. No

advertisement will be used for study recruitment. Subjects will undergo an informed consent process in accordance with GCP. Informed consent will be obtained prior to the performance of any screening procedures. Subjects must meet all of the inclusion and none of the exclusion criteria as determined by pre-treatment battery measures. The treating radiation oncologist will approach and inform the patient about the study, thereby initiating the informed consent process. If the patient expresses interest in the study, the treating radiation oncologist will contact a qualified member of the research team in the Radiation Oncology department at the University of Pennsylvania and initiate introduction to that team member. This research team member will interview the potential subject with privacy considerations, explain the requirements of the study and provide a copy of the Informed Consent Form. The volunteer nature of research will be stated and advice offered to the subject to take sufficient time to discuss the study if necessary before making their decision to sign the informed consent document. If a decision to participate is made, the informed consent form is signed after which any screening procedures will be performed. A series of questions will be asked to verify patient eligibility based upon the inclusion/exclusion criteria. After the eligibility is established, a subject study number will be issued. Eligibility is confirmed with the study investigator. All members of the research team will have successfully completed patient oriented research training. **Subjects will receive all radiation treatment in the Radiation Oncology clinic of the University of Pennsylvania.**

Normal participants will be recruited from the family, friends, and community members of the patients in the Department of Radiation Oncology. This technique was used previously in our studies of longitudinal effects of (photon) radiotherapy, and of normal aging. It has also been found to be successful in achieving target recruitment goals, in achieving the objective of matching patients with normals by age and education, and in recruiting normal who are generally from the same socioeconomic and cultural group as patients.

Normal subjects who volunteer to participate will be given brief interviews to identify their age and education, histories of developmental delays, learning difficulties, head injury, current psychiatric treatment, or a medical disorder that could affect learning, and medications currently being taken. Inclusion criteria are based on the age, education, and gender of the combined patient cohorts, so that the normal subject mean on these variables will not be significantly different from the patient cohort overall mean. Normal subjects must use English as their primary language or be bilingual in English. Exclusion criteria are histories of developmental delays, dyslexia or other learning disability, head injury, neurological disorder, other medical disorder than affects learning, current psychiatric treatment, complaints of major memory difficulty, and current use of medications for one of these disorders.

Early Withdrawal of Subjects

When and How to Withdraw Subjects

Study subjects may be withdrawn from the study prior to the expected completion for the following reasons:

Study subjects showing disease progression.

Study subjects expressing a wish to discontinue study participation.

Study subjects unable to comply with the time and immobilization needs of the MRI studies.

Data Collection and Follow-up for Withdrawn Subjects

The study data for withdrawn subjects will be analyzed. Withdrawn subjects will continue to be followed according to the routine follow-up schedule for their oncologic care. As survival is not a study endpoint, and the

study does not involve a therapeutic intervention, survival data for withdrawn subjects will not be formally collected as a study requirement.

Study Procedures

See Section 3 for description of specific neurocognitive testing and MR imaging and procedure table.

Visit 1 (before the start of radiation therapy)

Study subjects will have a baseline research neurocognitive evaluation, anticipated to require approximately 4-5 hours. MRI study acquiring anatomic, perfusion, spectroscopy, and diffusion is anticipated to require approximately 60 minutes.

Visit 2 at approximately 1.5 months after completion of radiation for both cohorts, same procedures as above.

Visit 3 at approximately 6 months after completion of radiation for both cohorts, will undergo the same procedures as above.

Visit 4 at approximately 12 months after completion of radiation therapy for both cohorts, will undergo the same procedures as above.

Visit 5 at approximately 24 months after completion of radiation for both cohorts, will undergo the same procedures as above.

Primary and secondary endpoints will be acquired at all time points

6.0 STATISTICAL PLAN

6.1 STUDY DESIGN

This is a longitudinal, observational study of brain imaging and neurocognitive testing in patients with either head and neck/skull base tumors (benign or malignant) or low grade glioma or meningioma who are receiving radiation therapy. Patients will be stratified by site of disease. **The over-arching hypothesis is that dose reduction to normal brain tissue provided by proton therapy will reduce both brain injury and neurological deficits.**

We will enroll 20 patients with head and neck/skull base tumors (benign or malignant) who are being treated with protons over 3 years. Prior to the activation of the proton clinical trial, approximately 10 patients being treated with photons will be enrolled and will serve as contemporary controls.

We will enroll 40 patients with low grade glioma or meningioma who are being treated with protons over 3 years. The proton clinical trial is already activated and all low grade glioma or meningioma patients treated by the Department will be treated with protons. Two historical cohorts of 40 PENN glioma patients treated with photons and 30 untreated PENN glioma patients, who had neurocognitive testing on the identical schedule, will serve as the control groups.

Neurocognitive test data will be collected from the normal normal group (70 patients) only for the four tests of cerebellar-specific function: Audio-Visual Attention Shifting Test, Serial Response Task, Balls in a Bottle Test, and Timing Functions Test. The values from the normal group will add to the longitudinal analyses by permitting us to describe a level of clinical impairment, if any, in the patients at the longitudinal time points.

6.2 OBJECTIVES (FOR BOTH COHORTS)

1. Assess cognitive changes over three years, within and between patient groups, with analyses within the first year, and at years two and three.
2. Examine other clinical variables that may exacerbate (or protect) patients from functional damage from irradiation.
3. Investigate the association of specific cognitive variables with associated imaging regions of interest.

6.3 ENDPOINTS

6.3.1

Structural imaging variables, see Sections 3.4.1.-3.5.

Neurocognitive variables, see Section 3.5.1.

6.3.3 Assessment Times

Neurocognitive tests will be performed at approximately: baseline (prior to radiotherapy), 1.5 and 6 months after completion of radiation and then annually approximately at 12 and 24 months for both cohorts. MRI testing will be performed for both cohorts at approximately : baseline, 1.5, 6, 12 and 24 months after completion of radiation treatment.

6.3.4 Baseline and Treatment Variables and Time varying Covariates

Baseline and treatment variables, such as age, radiation dose, treatment volume, will be included. Medications will be coded as four dichotomous time varying covariates: anti-hypertensives, anti-seizure, steroids and anti-depressants.

6.4 STATISTICAL ANALYSES (FOR BOTH COHORTS)

General Methods: Graphical methods, including histograms, scatterplots, boxplots, and mean plots of time trends will be generated, to understand data quality and variability. Mean, median, range, and standard deviation will be computed for all continuous variables. Frequencies and percentages will be computed for categorical and ordinal variables. Prior to hypothesis testing and modeling, we will consider transformation to Z-scores for scales for which population normative values are well established. For variables that exhibit markedly skewed distributions, appropriate transformations, such as natural logarithm, will be applied. Pearson's correlation will be employed to assess correlation between imaging and neurocognitive measures taken at the same time points.

Hypothesis Testing: Neurocognitive function, memory in particular, significantly declined from baseline to 1.5 months post-completion of radiotherapy in low grade glioma patients treated with photons. A gradual rebound beginning 6 months post-completion of radiotherapy and continuing through at least one year of follow-up was observed. We hypothesize that in proton-treated patients, the decline at 1.5 months will be reduced, and that larger positive slopes of change in cognitive function will emerge by the last study time point, two years post treatment (one or two years post treatment in some patients recruited later in the study).

For Aim 1, a primary objective is to evaluate within-patient changes from baseline to one year. For the proton-treated group, within-patient change will be tested by paired t test. Within-patient trends over time will be analyzed with linear mixed effects models. To model the early decline and then rebound, piecewise linear or quadratic functions will be evaluated. Linear mixed effects models are available in several statistical software packages, such as the *xtmixed* procedure in STATA. Missing data are common in longitudinal studies. The *xtmixed* procedure allows unbalanced data, enabling us to analyze all data collected. In addition, we will assess the impact of the missing data on model estimates by conducting sensitivity analyses that make different assumptions about the missing data mechanism. For example, we will use multiple imputation to impute missing values assuming a missing at random (MAR) mechanism, that allow missing data to depend on measured variables such as age and sex. Another primary objective is to evaluate between-group differences in these changes from baseline to one year,

which will be assessed by independent groups t test or by repeated measures ANOVA. Trends over time will be compared among the untreated, photon and proton radiation groups using linear mixed effects models, in which a time by group interaction term is included. The analysis strategy described above will also be applied to longitudinal brain imaging data.

For Aim 2, to examine clinical variables that may exacerbate (or protect) patients from functional damage, linear mixed effects models will be extended to include baseline fixed effects and time varying covariates.

For Aim 3, to investigate the correlation between longitudinal neurocognitive measurements and longitudinal brain imaging measurements which are measured at the same time points, linear mixed effects models will include repeated brain imaging outcomes as random effects.

6.4 SAMPLE SIZE/POWER

6.4.1 Skull Base

With 20 proton patients enrolled, a within-patient change of 0.85 SD_{diff} units between baseline and 1.5 months post-completion of radiation, can be detected with 81% power by paired t-test at a reduced 2-sided 1% significance level. With 20 proton patients and 10 photon patients, a difference in mean change from baseline to 1.5 months of 1.5 SD units between groups can be detected with at least 85% power by 2 independent group t-test at a 2-sided 1% significance level.

There are no preliminary longitudinal neurocognitive data in skull base patients treated with photons or protons. Comparison of slopes will also be tested with a linear mixed effects model. If we find that the trend is linear throughout the entire time interval from baseline, then the model will include 5 repeated measures. Otherwise, assuming the linear mixed model is focused on the rebound in the time interval from 1.5 to 24 months post-radiation, and the following inputs: 15 patients per group, 4 repeated measures, 0.01 type I error, 80% power, correlation = 0.5, $SD_x^2 = 100.5$ and $SD_y^2 = 12.5$, an effect size of 0.18 words/month can be detected. Because of the smaller sample size in this group and our lack of preliminary data, these analyses will be more exploratory and focus on estimation of trajectories over time rather than hypothesis testing.

6.4.2 Low Grade Glioma or Meningioma

With 40 proton patients enrolled, a within-patient change of 0.6 SD_{diff} units between baseline and 1.5 months post-completion of radiation, can be detected with 85% power by paired t-test at a reduced 2-sided 1% significance level to control for multiple comparisons arising from many neurocognitive tests. With 40 proton patients and 40 historical photon patients, a difference in mean change from baseline to 1.5 months of 0.8 SD units between groups can be detected with 82% power by 2 independent group t-test at a 2-sided 1% significance level. Comparison of 40 proton patients to 30 untreated controls would have 80% power to detect a 0.85 SD unit difference.

We have preliminary longitudinal data on the ‘Delayed Recall Word List’ memory test from 40 photon radiated glioma patients and 30 untreated glioma patients (Armstrong et. al. manuscript in progress). Patients were given this memory test at baseline and at 1.5, 6 and 12 months after completion of radiation. The patients were asked to memorize a list of 15 words. After a time delay, they were then asked to recall the word list. The grand mean \pm SD of the number of words recalled, for all 70 patients pooled over all time points was 10.38 ± 3.54 words ($SD^2 = 12.53$). Data for each group at each time point were:

| Observed values | | Months from the completion of radiation | | | |
|-----------------|-----------|---|-------|-------|-------|
| | | baseline | 1.5 | 6 | 12 |
| Mean # words | Radiation | 10.20 | 8.45 | 9.53 | 10.69 |
| | Untreated | 11.45 | 11.33 | 11.72 | 11.47 |

If proton therapy reduces neurological deficits as expected, then the proton group may exhibit little change in memory function, similar to the untreated group.

In a linear mixed effects model, the comparison of slopes would focus on the gradual rebound in the time interval from 1.5 to 24 months from completion of radiation. Using the formula on page 30 of Diggle et. al. *Analysis of*

Longitudinal Data, an R program was written to calculate effect size. The table below displays detectable effect sizes (i.e., difference in slopes between two groups) assuming the following inputs: 40 patients per group, 4 repeated measures, 0.01 type I error, 80% power, correlation = 0.5, $SD_X^2 = 100.5$ (from time points 1.5, 6, 12 and 24 months from end of radiation) for a range of values of SD_Y^2 .

| Variance of outcome, SD_Y^2 | Detectable Effect size (words/month) |
|-------------------------------|--------------------------------------|
| 8 | 0.09 |
| 10 | 0.10 |
| 12 | 0.11 |

Assuming variance of 12, slope = 0 for proton patients, a model of slopes over the 1.5 to 24 months from completion of radiation interval and slope = 0.11 words/month for photon patients, the expected between-group differences are shown in the table below.

| Expected values | | Months from the completion of radiation | | | |
|--------------------------|--------|---|------|------|------|
| | | 1.5 | 6 | 12 | 24 |
| Mean # words | Photon | 8.5 | 8.8 | 9.7 | 11.0 |
| | Proton | 11.5 | 11.5 | 11.5 | 11.5 |
| Between-group Difference | | 3.0 | 2.7 | 1.8 | 0.5 |

7 Safety and Adverse Events

7.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An *adverse event* (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A *serious adverse event* is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above.

All adverse events that do not meet any of the criteria for serious should be regarded as *non-serious adverse events*.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

7.2 Reporting of Serious Adverse Events and Unanticipated Problems

7.2.1 IRB Notification by Investigator

All events meeting the Penn IRB SOP for Unanticipated Events posing risks to subjects or others will be reported to the IRB as follows:

Unanticipated problems are:

(1) Unforeseen; and (2) indicate that participants are at increased risk of harm. The IRB requires investigators to submit reports of the following problems within 10 working days **with one exception**. The one exception for prompt reporting within 10 days applies to death of a research participant as noted below.

Adverse Event (regardless of whether the event is serious or non-serious, onsite or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is both unexpected and related to research procedures.

Note: An event is “unexpected” when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts); An event is “related to the research procedures” if the event is deemed probably or definitely related.

Reporting Deaths: more rapid reporting requirements

Concerning deaths that occur during the course of a research study, the following describes the more rapid reporting requirement of the Penn IRB for specific situations:

- Report the event within 24 hours when the death is unforeseen (unexpected) and indicates participants or others are at increased risk of harm.
- Report the event within 72 hours, for all other deaths, regardless of whether the death is related to study participation.

For reportable deaths, the initial submission to the Penn IRB may be made by contacting the IRB Director or Associate Director. The AE/Unanticipated Problem Form is required as a follow up to the initial submission.

7.2.2 Data and Safety Monitoring Committee (DSMC) Notification by Investigator

All Serious Adverse Events (SAEs), regardless of grade, expectedness or attribution must be reported to the DSMC within 30 days. Deaths that are possibly, probably or definitely related to the protocol treatment/experience must be reported within 24 hours. SAEs should be reported to the DSMC for six months from the date the last subject was treated.

7.2.3 USAMRMC, Office of Research Protections, Human Research Protection Office Notification (ORP, HRPO) by Investigator

All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study should be promptly reported by phone (301-619-2165), by email (hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

7.3 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events. "The medical monitor will provide an unbiased written report of the event to include comment on the outcomes of the event or problem and in the case of a serious adverse event or death, comment on the relationship of the event to participation in the study. The medical monitor must also indicate whether she/he concurs with the details of the report provided by the principal investigator".

The Medical Monitor will be Amy Pruitt, MD (a physician who is not directly involved in the trial and is not collaborating with the sponsor/investigator in any other trial). Because of Dr. Pruitt's background and experience she is an appropriate Medical Monitor (MM) for this study. In the role, she will review all AEs including grading, toxicity assignments, dose modifications, and all other safety data and activity data observed in the ongoing clinical trial along with discussing relevant animal and toxicology studies and similar investigational agents. The Medical Monitor may recommend reporting of adverse events and relevant safety data not previously reported and may recommend suspension or termination of the trial. The investigator will meet with the Medical Monitor every year. Serious and unexpected issues will be handled on an ad hoc basis through calls or e-mail. Documentation of Medical Monitor activity will be maintained in the study specific Regulatory Binder. Copies of a Medical Monitor report requiring action on the part of the PI to protect subject safety or study integrity must be submitted to the DSMC within 10 business days.

7.3.1 Data and Safety Monitoring Committee

The University of Pennsylvania Cancer Center (UPCC) through the Data and Safety Monitoring Committee (DSMC) will be reviewing this clinical trial. It is anticipated that with approval, the committee's role will be to ensure that the rights and well-being of all subjects are protected and that patients are treated in full compliance with the study treatment and parameters specified in the protocol. The Data and Safety Monitoring Committee (DSMC) is responsible for overseeing the process of monitoring of studies and the conduct of audits. The investigators on this study are responsible for the continuous, close monitoring of subjects enrolled on this trial.

A Medical Monitor, Amy Pruitt, M.D., who is not directly involved in this trial and is not collaborating with the investigator in any other trials, has been selected for this trial. The Medical Monitor will review adverse events, safety data, and activity data observed in the ongoing clinical trial. The Medical Monitor may recommend reporting of adverse events and relevant safety data not previously reported, and may recommend suspension or termination of the trial. The summary reports of all discussions of adverse events will be submitted to the Data and Safety Monitoring Committee (DSMC) on an annual basis or more frequently if appropriate.

The Principal Investigator or his/her designee of the trial will present to the Medical Monitor all adverse events observed inpatients, any activity data obtained, and whether those data invoked any stopping criteria in the clinical protocol. Adverse event reporting will follow the NCI guidelines. Results of the data from toxicology or other animal studies that are relevant will be discussed. Other information related to the safety and efficacy of the clinical study will be discussed. This includes information of similar investigational materials used in different studies.

7.4 Protocol Deviations/Exceptions

Occasionally, the investigator may need to deviate from the approved protocol. Deviations are categorized as reportable and non-reportable. Reportable deviations may be urgent or not. Urgent deviations may occur on the spot as necessary to protect the safety of a study subject and do not allow enough time for reporting in advance. However, they must be reported as soon as possible.

All deviations from the study protocol will be handled as follows:

7.4.1 Eligibility

Deviations from established eligibility criteria will not be allowed. If the investigator believes that a subject would truly benefit from the protocol therapy and there are no other viable options, then the protocol should be amended to reflect the change in restrictions. There may be situations where the deviation from eligibility may not warrant a study amendment (e.g. a necessary test/procedure being a few days outside of the eligibility window, subject taking a concomitant medication within recent timeframe etc.). These deviations must still be reviewed and approved in advance of enrolling the subject.

The IRB must be notified of the planned deviation and a copy of all applicable amended study documents must be sent to the IRB. The planned deviation must also be submitted to the DSMC for evaluation. The DSMC does not approve deviations but rather provides an unbiased assessment of the appropriateness of the request. Both committees must be given sufficient time to review the request, gather additional information as necessary and make

a decision. The Medical Monitor will be consulted first for all such deviations. Documentation of the Medical Monitor's assessment and opinion will be included with the initial report to both committees.

7.4.2 Other Reportable- Deviations that affect the protocol treatment administration (i.e. dose administered, route/method of administration etc.), dose adjustment schema, stopping rules, modification to follow-up, removal of safety assessments/follow-up visits, accrual goal or any deviation that may affect the study outcome analysis or study integrity must be approved by the IRB and reviewed by the DSMC.

7.4.3 Non-Reportable- During the course of a study, there may be times when deviations are outside of the control of the investigator (i.e. subject not showing up for a study visit, lab errors, subject confusion etc.). These type of deviations are not reportable (unless they occur at a level that impacts any of the reportable categories) but must be documented in a timely manner to show the impact of the deviation and corrective/follow-up actions that were taken. Documentation can be in the clinic/progress notes or note/memo to file. Notes/memos should be signed and dated.

7.4.4 Reporting Deviations/Exceptions

Reports to the IRB and DSMC will be done via the electronic Clinical Trials Management System, Velos. Reportable deviations must also be sent to the study Medical Monitor (if applicable). A report will also be filed to USAMRMC, Office of Research Protections, Human Research Protection Office.

8.0 Data Handling and Record Keeping

All patients must have a signed Informed Consent Form and an On-study (confirmation of eligibility) form filled out and signed by a participating investigator prior to entering the study.

Confidential research charts will be kept in locked cabinets at each participating institution. Subjects will be assigned a study number at the time of study enrollment. This study number and not the subject's name will be used on all case report forms.

8.1 HIPAA Compliance:

Patients will be asked to read and sign a combined informed consent form and HIPAA authorization form acknowledging the uses and disclosures of protected health information (PHI) in this study as required by The Health Insurance Portability and Accountability Act (HIPAA). PHI will not be shared with any outside institution except as required by law. Any reporting of the results of this study will be done only with de-identified patient data. Confidentiality will be protected as outlined below.

- Each subject will sign a study combined informed consent and HIPAA authorization form prior to study enrollment.
- Each subject will be assigned a study number. All research-related material (to include specimens for research) will be labeled with the subject study number and the subject's initials.
- A list of the subject names with the associated subject numbers will be maintained in a locked cabinet and computer by the principal investigator and study coordinator.
- All research subject records will be kept in a study chart or in the electronic CTMS, Velos.

8.2 Data Entry

All patients must have a signed Informed Consent Form and an On-study (confirmation of eligibility) form filled out and signed by a participating investigator prior to entering the study. Case report forms will be used to standardize data-keeping.

8.3 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 subject(s) 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.

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 (i.e. that the subject is alive) at the end of their scheduled study period.

8.3.1 Unintentional Disclosure

Upon discovering that PHI may have been or has been disclosed to anyone not specified in the HIPAA disclosure consent, the investigator will report the disclosure to the Institutional Officer in the Office of Research Compliance and Integrity. The report should contain details about the type of data disclosed and the extent of the disclosure (number of subjects, who received it etc.). A report will also be filed to USAMRMC, Office of Research Protections, Human Research Protection Office.

8.4 Records Retention

8.4.1 Federally Funded Research or Non-IND/IDE Research

The DHHS regulation (45 CFR 46.115) states that records relating to research conducted or supported by any Federal department or agency shall be retained for at least 3 years after completion of the research.

The FDA regulation (21 CFR 56.115) is virtually identical; it also states that IRB records must be retained for at least 3 years after completion of the research for these same types of studies.

Records for this study will be maintained in a secure location with access limited to the investigators and the study specific research team for 3 years from the date of full study terminations. If necessary, after the first year of termination, records may be moved to an off-site secure storage facility.

8.4.2 HIPAA Retention Period (45 CFR164.530(j):

Protected Health Information (PHI) Research Requests (HIPAA1-008): Records documenting research requests, privacy board review or privacy officer expedited review, background material, and acceptance or denial of request. Retain 6 years after research completed.

Protected Health Information Disclosure Records (HIPAA1-009): Documenting the release of PHI, including **both authorized and unauthorized** releases. Should include the date of release, to whom the information was released, and the circumstances of the release. Retain 6 years after research completed.

Maintenance of HIPAA records is independent of the regulations for clinical study records. All records of PHI research requests and any type of release will maintained for 6 years after the research is fully terminated.

9 0 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

The study PI is responsible for ensuring the ongoing quality and integrity of the research study. In addition, this study will be monitored or audited in accordance with Abramson Cancer Center's NCI approved Institutional Data and Safety Monitoring Plan.

The University of Pennsylvania Cancer Center (UPCC) has a formal plan for Data Safety and Monitoring of Clinical Trials. The clinical trial, "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" is a trial that is subject to oversight of the UPCC through the Clinical Trials Scientific Review and Monitoring Committee (CTSRMC). The CTSRMC role is to ensure that the rights and well-being of all subjects are protected and that

patients are treated in full compliance with the study treatment and parameters specified in the protocol. The Data Safety Monitoring Committee (DSMC) is responsible for overseeing the process of monitoring of studies and the conduct of audits. The investigators on this study are responsible for the continuous, close monitoring of subjects enrolled on this trial.

9.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

A DSMC audit of this trial will be performed twice a year for as long as the trial remains open for accrual. However, this schedule may be changed at the discretion of the DSMC. High enrolling or quick enrolling studies will be audited more frequently as necessary. Investigators are notified in advance of the selection of their protocol for review and cases are randomly selected. Three randomly selected subjects or 10% of the total accrual (up to 10 subjects), whichever is higher, are audited. A formal report is written to the PI within about 5 business days of the audit. The committee may alter the frequency of re-monitoring based on the audit findings and degree of deficiencies. If an audit is unacceptable due to major deficiencies, representatives from the DSMC meet with the PI to discuss the findings of the audit and necessary corrective actions. If the deficiencies involve subject safety or serious regulatory violations, the Cancer Center Director, DSMC Chair, and DSMC Administrative Director will meet to discuss necessary actions concerning study status. The PI is given five business days to respond to these finding. An evaluation of the deficiencies will be re-evaluated upon receiving the PI's response. At this time, if the DSMC Chair and the Administrative Director do not find the response satisfactory, the IRB and OHR will be alerted of the actions taken by the ACC. The DSMC Administrative Director will update the IRB and OHR of the corrective actions being taken and progress being made.

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be maintained in the study specific Regulatory Binder which contains "Essential Study Documents". In addition, NCI requires all cancer based studies to have an independent scientific review. This protocol must be reviewed and fully approved by the Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) prior to enrolling any subjects. Documentation of CTSRMC approval must also be maintained in the study specific Regulatory Binder.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB and CTSRMC for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed and dated by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

11 Study Finances

11.1 Funding Source

This study is being funded by a grant from the Department of Defense (DOD) Telemedicine and Advanced Technology Research Center (TATRC)

12 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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Attachment A

Protocol Addendum

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

The following are reporting requirements and responsibilities of the Principal Investigator to the United States Army Medical Research and Materiel Command's (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO).

- (1) The protocol will be conducted in accordance with the protocol submitted to and approved by the USAMRMC ORP HRPO and will not be initiated until written notification of approval of the research project is issued by the USAMRMC ORP HRPO.
- (2) Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command as a part of their responsibility to protect human subjects in research. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information.
- (3) All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study should be promptly reported by phone (301-619-2165), by email (hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.
- (4) Any deviation to the protocol that may have an effect on the safety or rights of the subject or the integrity of the study must be reported to the USAMRMC ORP HRPO as soon as the deviation is identified.
- (5) Major modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the USAMRMC ORP HRPO for approval prior to implementation. All other amendments will be submitted with the continuing review report to the USAMRMC ORP HRPO for acceptance.
- (6) A copy of the approved continuing review report and the local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available. A copy of the approved final study report and local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available.

Attachment B

Glomerular Filtration Rate (GFR) Calculation

Glomerular filtration rate (GFR) is the best overall index of kidney function. Normal GFR varies according to age, sex, and body size, and declines with age.

In adults the best equation for estimating glomerular filtration rate (GFR) from serum creatinine is the Modification of Diet in Renal Disease (MDRD) Study equation. The original MDRD Study equation GFR Calculator is for use with routine creatinine methods. The IDMS-traceable MDRD Study equation GFR Calculator is for use with those methods that have been recalibrated to be traceable to IDMS.

http://nkdep.nih.gov/professionals/gfr_calculators/orig_si.htm

Appendix III: Walter Reed 2014 Summary

Research effort in 2014 for Phase 6 was divided in two parts. The first tested and developed dosimetry procedures using radiochromic film in a moving solid water phantom. The second part developed and tested a thorax phantom that incorporated motion and tissue heterogeneities. The 3D printer generated thorax phantom portion of the thorax phantom was built by Dr. Peter Liacouras in the 3D Medical Applications Department. The phantom will be planned using the ECLIPSE Treatment Planning system at WRNMMC and tested using the photon machines in the Radiation Oncology Department at WRNMMC. Ultimately, the thorax phantom and simulated lung and tumor movement will be tested at University of Pennsylvania Roberts Proton Facility.

A comment on multichannel dosimetry (directly to my accepted article in Medical Physics) will be published shortly in Medical Physics.

A point by point response has been sent to Physics in Medicine and Biology for my submitted article on using radiochromic film as an areal detector LET.

Summary for Dosimetry for Solid Water and Radiochromic film

This preliminary summary provides background for proton dosimetry that will eventually evaluate the accuracy and precision of treatment planners and radiochromic film dosimetry. The summary evaluates the ECLIPSE photon dose distribution from the 6 MV WRNMMC Trilogy machine onto a moving solid water phantom and stationary phantom. A virtual ITV was generated using the 4D CT (for “Large Amplitude” motion) and plans using IMRT, Arc rotations and 6 sets of static field sizes (“3D”) plans were generated. To help illustrate the experimental configuration, the axial and coronal views of the ECLIPSE ARC therapy are shown in Figures 1,2. Previously the temporal aspects were discussed regarding the 3D Linear drive and lung tumor motion. The virtual elliptical ITV and cylindrical lung tumor are also shown in the Figures 1,2.

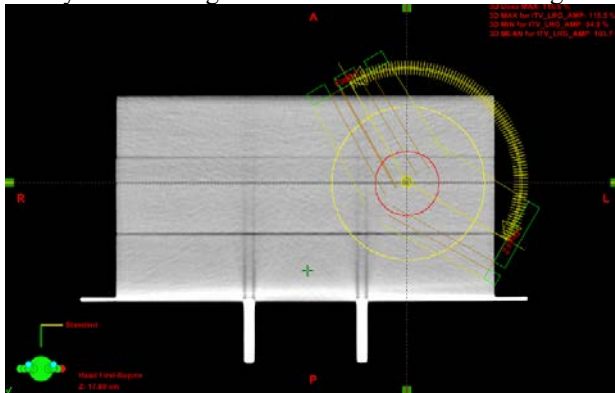


Figure 1 Axial view of ECLIPSE plan for Arcs for phantom undergoing Large amplitude motion

The CTV is a sphere and the motion was captured by contouring the virtual sphere for all 10 phases. The virtual lung was considered to be stationary and roughly replicated the size of a single lung. The movement was intended to emulate the Large Amplitude (LA) lung tumor motion typical of a tumor located close to the diaphragm and described in an earlier email derived from Seppenwoode et al. . In addition, dose calculations and measurements were generated for a static phantom.

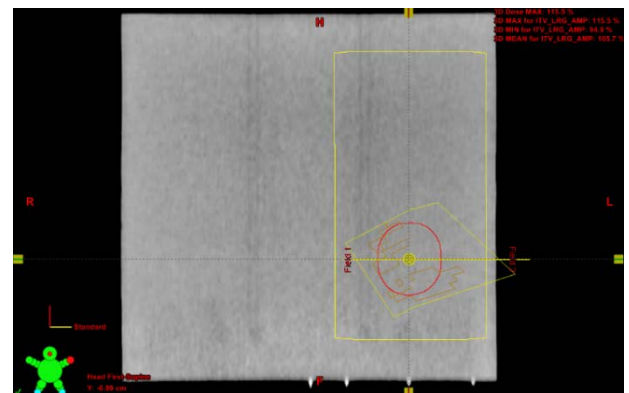


Figure 2 Coronal view of ECLIPSE plan for phantom undergoing Large Amplitude motion

Gamma analysis is used to compare the measured dose distribution and the calculated dose distribution. Gamma analysis evaluates every pixel within a given area (in this case ITV and the Lung-ITV). The computations determines if a pixel within a certain distance (3 m or 5 mm) has a similar doses within 3%. If the difference in doses fall s outside the three (two spatial dimensions, and dose) dimensional ellipsoid, then there is a discrepancy. The

calculated and measured dose distributions are registered to the pixel level i.e. the two images have the same spatial resolution and have been rotated and translated to match each other based on fiducial markers.

Below are the two dimensional dose distributions generated by the ECLIPSE planner and the dose measured with the radiochromic film. The radiochromic film dose distribution was generated using an optimized multichannel approach.

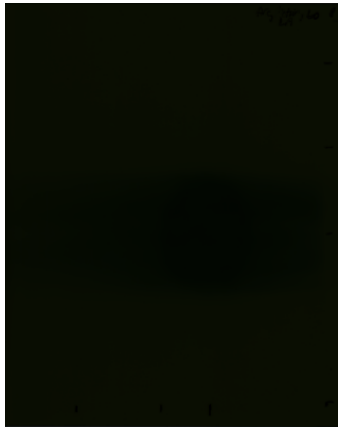


Figure 3 Exposed Radiochromic film from ARC therapy for Large Amplitude motion

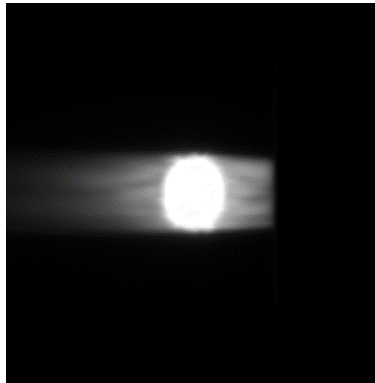


Figure 4 ECLIPSE dose distribution for ARC plan applied to large motion phantom

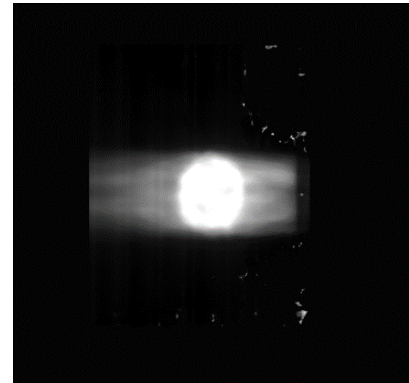


Figure 5 Measured dose distribution of ARC plan applied to large motion phantom taken from radiochromic film using optimized multichannel approach and registered to the ECLIPSE plan.

The virtual ITV (from 4D CT) (ellipsoidal shape of 5.0 and 5.6 cm diameters, shown in

red) and the virtual lung (rectangular shape of 12 cm x 22.5 cm with an ellipsoid removed, shown as magenta) were used to assess the dosimetry for phantoms undergoing large amplitude movement and treatment plans and shown below. The ITV has 5376 pixels and the lung minus the ITV contains 47,920 pixels. For static phantom, a CTV or circle of 5.0 cm diameter (4777 pixels) and lung minus circle area has 48,047 pixel

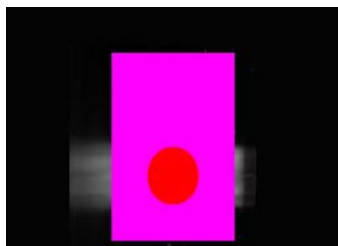


Figure 4 Virtual ITV and lung superimposed on treatment plan

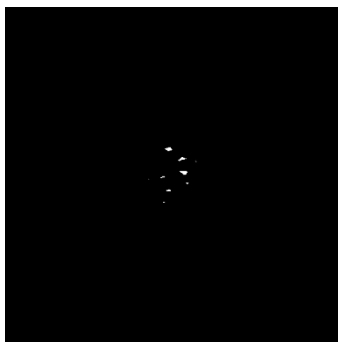


Figure 5 Gamma Exceedances for 5 mm and 3% dose criteria for ITV

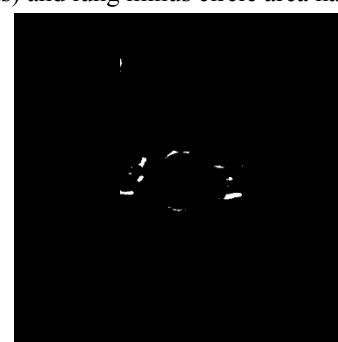


Figure 6 Gamma Exceedances for lung minus ITV using 5 mm and 3% dose criteria

A summary table showing the percent of gamma exceedances

| Type of Exposure | Area | Gamma Exceedances (%) 3 mm, 3% Dose | Gamma Exceedances (%) 5 mm, 3% Dose |
|------------------|----------|--|--|
| 3D LA | ITV | 0 | 0. |
| | Lung-ITV | 0.68 | 0 |
| 3D Static | CTV | 0.19 | 0 |
| | Lung-CTV | 16.8 | 10.8 |
| ARC LA | ITV | 25.8 | 10.7 |
| | Lung-ITV | 2.59 | 0.84 |
| Arc Static | CTV | 15.3 | 9.02 |
| | Lung-CTV | 7.47 | 2.39 |
| IMRT LA | ITV | 8.98 | 1.77 |
| | Lung-ITV | 1.44 | 0.582 |
| IMRT Static | CTV | 37.1 | 26.5 |
| | Lung-CTV | 13.5 | 9.95 |
| | | | |

A more conventional way to display the comparison between the ECLIPSE and measured dose distribution is to show dose profiles. The red arrows in the figures show the profiles for both the horizontal and vertical profiles for the ECLIPSE and radiochromic film distributions for the static ARC configuration (the case displaying the worst gamma analysis)

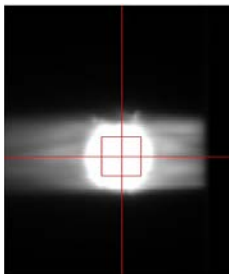


Figure 7
ECLIPSE dose distribution for ARC deposited on static phantom

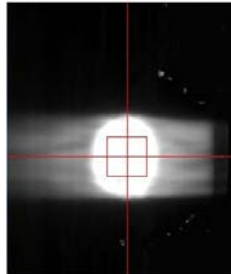


Figure 8
Radiochromic Film dose distribution from Arc and static phantom

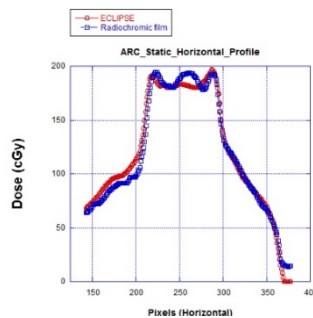


Figure 9 Horizontal dose profile for ECLIPSE and measured dose distribution for ARC plan and static phantom.

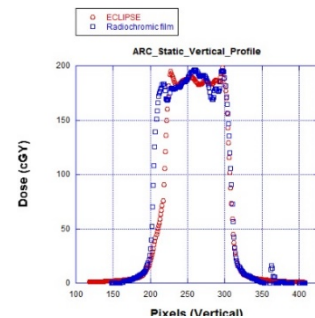


Figure 10 Vertical dose profile for ECLIPSE and Measured dose distribution form ARC and static phantom.

The tumor motion during a typical DIBH was also generated with the 3D Linear Drive. The motion incorporated by the fast change in position and slow decay to a plateau region.

| Type of Exposure | Area | Gamma Exceedances (%) 3 mm, 3% Dose | Gamma Exceedances (%) 5 mm, 3% Dose |
|------------------|----------|--|--|
| 3D DIBH | CTV | 2.85 | 1.17 |
| | Lung-CTV | 10.4 | 3.03 |
| ARC DIBH | CTV | 5.67 | 0.033 |
| | Lung-CTV | 15.5 | 7.12 |
| IMRT DIBH | CTV | 15.4 | 5.19 |
| | Lung-CTV | 2.35 | 0.63 |

From examining the large amplitude, static, and DIBH motion it appears that

1. Gamma analysis results degrade at the sharp interfaces. Motion tends to create fuzzy edges and any misregistration between the ECLIPSE plan and the radiochromic film is reduced.
2. The sharp corner in the rectangular phantom seems to degrade agreement in the ECLIPSE plan and measured dosimetry as evidenced by the better performance of the 3D plan and measured dosimetry.

This manuscript describes the properties and construction of a thorax phantom with a moving surrogate tumor. A 3D printer generated the plastic chest wall, spine, and posterior regions of the phantom. The phantom is heterogeneous, its geometry closely resembles a patient. A surrogate tumor controlled by a 3D linear stage emulates lung patient movement. The lung material is sawdust permitting tumor motion and dosimetry within the tumor and surrounding lung.

Introduction, Background

Experimental validation of calculated external beam radiation therapy for treating cancer is an essential component for applying clinical radiation to tissues. Treating various sites such as lung tumors can be complicated by the presence of heterogeneous tissues within the radiation path as well as movement of the tumor and or surrounding tissues (Keall et al. 2006, Vinogradskiy et al. 2009). Often Monte Carlo calculations are used to support the approaches advanced by researchers and clinicians. Measuring the radiation dose deposition within surrogates such as within the phantoms are far less common (Nioutsikou et al. 2008, Steidl et al. 2012, Serban et al. 2008, Keshani et al. 2007). Although the phantoms can never absolutely simulate actual patients, they can validate, examine, and guide approaches under tightly controlled conditions.

The relatively new 3D printers have generated a variety of products for medical applications. Specifically custom plastic prosthetics, medical tools, molds, masks, and more recently phantoms (Yoo et al. 2011, Gear et al. 2014) can be accurately generated to fit individual needs. This short note describes a thorax phantom produced by a 3D printer that accurately mimics the geometry of a patient. In addition, a surrogate tumor produced by a 3D printer is precisely transported with a 3D linear stage within the thorax phantom and a simulated lung material. The lung tumor motion replicates typical motion in three dimensions of a patient with lung tumor in close proximity to the diaphragm. The lung portion of the thorax phantom, unlike most phantoms permitted measurements within the lung (as well as tumor).

A number of thorax phantoms permitting lung tumor motion have been discussed in the literature and are commercially available for clinical and research applications. For example, the CIRS thorax phantom is composed of solid materials, including the lung, that permits custom controlled “tumor motion”, independent of the simulated thorax. Film dosimetry is confined to the “tumor” and discrete point doses can be measured within the simulated thorax. More recently, Steidl {Steidl et al. 2012) developed a phantom that permitted independent motion of the

thorax and tumor for examining dose deposited by protons. Dose distribution was collected within the tumor. The lung tissue was simulated by air. Others have more realistically modeled a deformable lung using sponging and compressive devices (Keshani et al. 2007, Serban et al. 2008).

Materials and Methods

This mobile thorax phantom incorporates a number of novel components such as a thorax chest wall generated by a 3D printer, using material to fill and simulate the lung and that also permits tumor motion and dosimetry within the tumor and in the nearby lung.

Choice of Patient Motion

Earlier, researchers have surveyed lung tumor motion within a variety of patients using tumor tracking and imaging. For example, Seppenwoode et al. examined 21 patients and found a range of motion depending on its location. The largest amplitude motion occurred near the diaphragm and was dominated by superior to inferior motion. As the tumor motion migrates to more superior direction and away from the diaphragm, the overall motion amplitude is reduced and motion in the anterior-posterior direction plays a more dominant role. Seppenwoode's patient data clusters into three separate segments: Large, Middle, and Low amplitude motion corresponding to the tumors location within the lung. The patient data is summarized below.

| Size/Site | Patient # | Direction | Mean (mm) | Std (mm) |
|-----------------------|-----------|--------------------|-----------|----------|
| Large Amplitude/Lower | 8 | Lateral | 1.26 | 0.79 |
| | 8 | Superior-Inferior | 9.22 | 7.79 |
| | 8 | Anterior-Posterior | 1.69 | 1.07 |
| Mid Amplitude/Middle | 2 | Lateral | 0.65 | 0.64 |
| | 2 | Superior-Inferior | 5.90 | 7.35 |
| | 2 | Anterior-Posterior | 3.50 | 3.25 |
| Small Amplitude/Upper | 11 | Lateral | 1.31 | 0.96 |
| | 11 | Superior-Inferior | 2.76 | 2.22 |
| | 11 | Anterior-Posterior | 2.40 | 2.16 |

Only the “Large Amplitude” motion is discussed in this publication. The other motions (“Mid”, “Small”) were also coded and tested. In addition tumor tracking studies found a phase lag for motion between the Superior-Inferior and the Anterior-Posterior directions due to delays in between the diaphragm and chest wall resulting in a Lisajous type of motion pattern, rather than a simple line. A phase delay of 10 degrees was incorporated into the Large Amplitude motion.

Seppenwoode found that lung tumors motion predominantly follows a power law (power equal to 3) of a sinusoidal motion, rather than a simple sine (or cosine).

$$P = A \left| \sin \left(\frac{\pi}{T} + \phi \right) \right|^3 \quad (1)$$

P is the position of the tumor always positive due to absolute symbol, A corresponds to the amplitude for each orthogonal direction (see table for each direction), T is the period (4.22 seconds) and ϕ is the phase difference ($\phi=0$ for superior-inferior and left-right direction and 10 degrees for anterior-posterior direction) and vertical brackets denotes the absolute value.

The power law is followed for all amplitudes and is also incorporated into the coded motion.

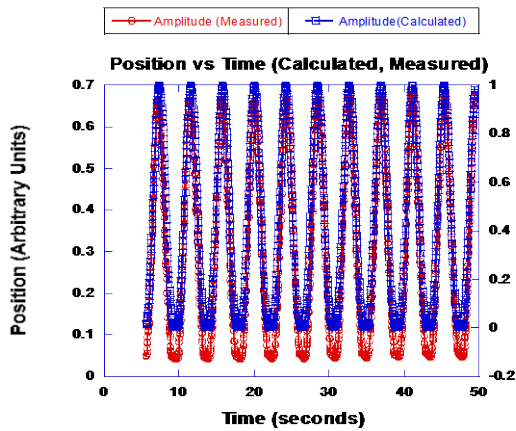
Motion Control

A Newmark Systems stepping motor controller (NSC-G3) manages three linear stages simultaneously (NSL4) also developed by Newmark Systems. The three independent and orthogonal linear stages precisely (0.03 microns)

transports a thin aluminum over a maximum distance of 5 cm and at a maximum rate of 12 mm/sec in a coordinated fashion as outlined above. The platform and motors are mounted onto a stationary aluminum plate. The controller communicates via RS232, Ethernet, and USB connections with the stages and laptop. Galil Tools software downloaded onto a laptop and interfaces with the controller. Custom programs are designed to emulate tumor motion. A long (35') cable connects the motion controller and the stages so that motion can be controlled in a shielded area while the motors and platform reside closer to radiation.

There were issues regarding missed steps and delays due to the "fast movement". Transporting the phantom at slightly slower speeds seems to correct many issues. There are no delays and the motion returns to its original spot after correcting for a small but repeatable hysteresis. However, vibration associated with the motion is still present, albeit at a reduced amplitude.

The temporal motion is followed either by attaching a bellows belt to the moving platform and a fixed point on the stage or an infrared reflecting box placed on the moving platform and followed with an infrared camera (Varian, RPM System). The temporal pattern from the RPM system is superimposed onto the calculated motion from Equation 1 in Figure 1a. A Fast Fourier analysis for the measured infrared detector as well as the calculation is shown in Figure 1b. Figure 1b shows the fundamental frequency (corresponding to period of 4.22 seconds) and the smaller second harmonic frequency component. Due to the absolute value (Equation 1) the largest component in the Fourier decomposition is a constant or zero frequency contribution. Both Figures indicate a close agreement in the measured and expected motions.



Thorax Chest Wall:

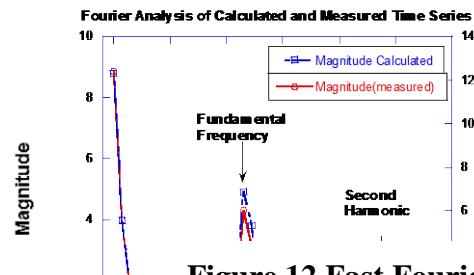


Figure 11: Time measured (RPM) and calculated Time (RPM) and calculated Time series shown in Figure 11 motion

3D printer

The template for the 3D printed thorax phantom was taken from a patient that had been treated for lung cancer. A sample axial slice is shown below.

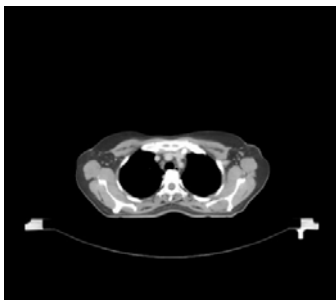


Figure 13 Axial view of a CT of lung tumor patient



Figure 14 Picture of 3D thorax phantom

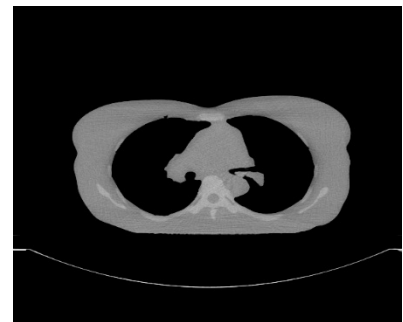


Figure 15 CT of 3D printer generated thorax phantom

The phantom is currently composed of two plastic materials to emulate soft tissue and bone. Tango Plus (83 HU) is used for the soft tissue and 8510 plastic for the bone (136 HU).

Various views of full scale thorax phantom sitting on CT scanner couch. A CT of the full scale, two-component thorax phantom is shown below.

The “soft-tissue” for the two-component 3D Printer thorax phantom follows roughly 70 to 90 HU. The bone follows 120-130 HU, lower than the human bone of 200-400 HU.

Lung Tissue Simulation

To simulate the lung, the material inserted into the lung cavity should have a number of desired attributes that resemble patient lungs. In addition the lung equivalent material permits the surrogate tumor and attached film to move within the cavity, in a relatively unperturbed fashion. Specifically, the material should have low density or low HU (-800 to -600 HU) and resemble, heterogeneous in density, HU (roughly emulating nodules, air, aerioles etc.), permit motion of the lung tumor via the 3D linear drive (soft, not-rigid), track the motion (stick to the tumor and radiochromic film), easily cleaned and removed from the plastic thorax phantom. The last feature is difficult to fulfill, especially during replacement of the radiochromic film. The Table shown below shows some candidate materials for simulating the lung.

This study examined a number of materials that may fulfill the requirements for lung substitute. Specifically, this study examine sawdust, dried banana, Cheerios breakfast cereal, pinto beans, pretzels, Cocoa Puffs breakfast cereal, Raisin Bran breakfast cereal (with and without the raisins), cotton, shaving gel, shaving cream, whipped cream, bean bags, brown sugar. The best candidates were sawdust, pretzels, whipped cream, Raisin Bran without the raisins.

| Material | Average HU | Standard Deviation HU |
|--------------------------------------|-------------------|------------------------------|
| Patient Lung | -787 | 72 |
| Sawdust | -795,-834 | 52,33 |
| Dried Banana | -558 | 209 |
| Cheerios | -862 | 47.35 |
| Pinto Beans | -173 | 261 |
| Pretzels | -736 | 133 |
| Cocoa Puffs | -849 | 73 |
| Raisin Bran (with raisins) | -541 | 298 |
| Raisin Bran (without raisins) | -796 | 112 |
| Cotton | -935 | 19 |
| Shaving Gel | -388 | 182 |
| Whipped Cream | -785 | 35 |
| Brown Sugar | -63 | 39 |

4D CT Scans of Thorax Phantom, mobile “tumor”, and Sawdust “Lung”

This is a description of a quick scan of the 3D Printer generated thorax phantom, plastic mobile “tumor”, radiochromic film, and sawdust “lung”. The “tumor” is composed of two hemispheres (sphere is 3.5 cm diameter, 22.4 cc, 8515 plastic, Hounsfield Unit 30) epoxied to a Cedar shim that act as a shaft. A slit was cut in the wooden shaft to permit insertion of radiochromic film. The film was 6 cm x 8 cm was the maximum permissible size without hitting the phantom walls during movement. The two halves of the plastic tumor were position sufficiently close to squeeze the radiochromic film. The cedar shaft (Hounsfield Unit -650 to -700) was screwed into the platform of the 3D Linear Stage. The film was positioned to measure the dose in the sagittal plane. The cedar shaft is screwed into the moving platform and the tumor, shaft, platform move in unison through the sawdust lung material.

The orientation of the film permits collection of the dose in the sagittal plane. Orthogonal sets of holes in the cedar shaft permit collecting dose in the coronal plane as well.

The tumor motion in three orthogonal directions was generated using previously described (“large amplitude”, 4.22 second period, sine³ motion, mostly superior-inferior direction) trajectory derived from patient data. Poster board was used to seal the opening for the left lung.

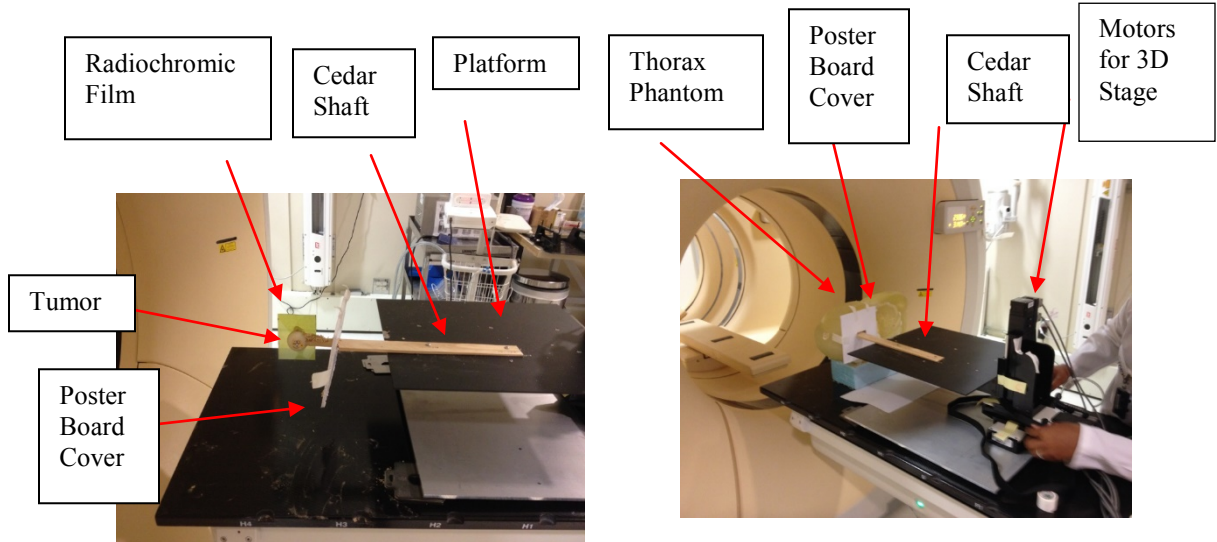
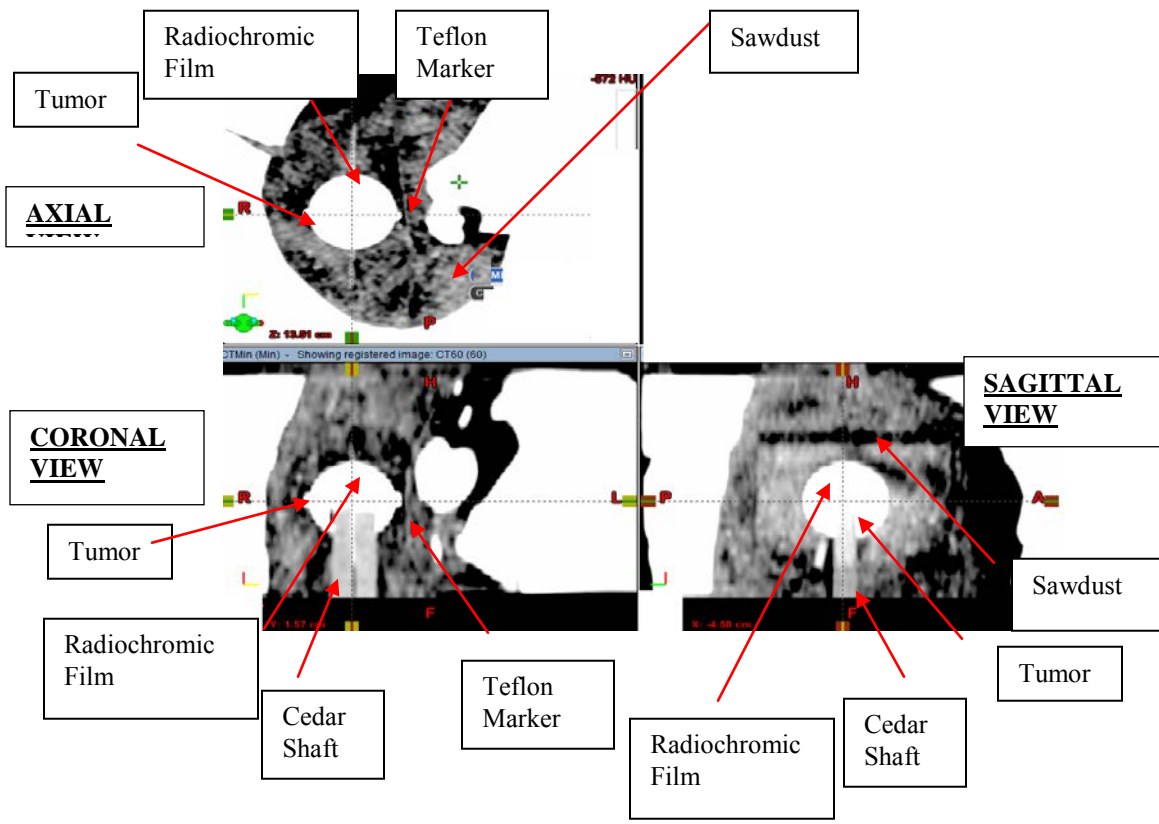


Figure 16 Picture showing mobile tumor arrangement, specifically of 3D linear stage, platform, cedar shaft, tumor, film

The cavity for the left “lung” was filled with sawdust using holes and openings in the poster board. Unfortunately it was difficult to fill the cavity (see CT images below and movies), especially in the anterior region. Due to limited visual access it was difficult to ensure that the cavity was filled unless the thorax was scanned.

The platform was aligned using shims placed under the platform legs and tested using a mechanical level. The platform was also aligned in the azimuthal direction using fixed positions on the platform to ensure that the CT axis is aligned with the platform. The tumor was aligned with CT scan lasers and Teflon markers placed on the tumor. Teflon markers were also placed on the thorax phantom.

Figure 17 CT of mobile tumor in thorax phantom (phase is 50 degrees). Three orthogonal views shown



The thorax phantom, tumor, radiochromic film, and sawdust were scanned. A 4D CT was generated with the aid of the bellows belt to monitor the motion generated by the 3D Linear stage. The CT images were transported to the ECLIPSE planning system and imported into ECLIPSE. Orthogonal views of the CT image are shown below.

4D CT Scan and Images

The 4D CT divides the time interval generated by the Belt signal or reflected infrared signal into 10 equal phases and can depict movement via the “movie mode”. The Teflon marker is visible in all modes and the movement of the Teflon markers is tracked with the ECLIPSE spatial marker tools. The position of the markers under programmed sinusoidal motions is shown in all three directions. As noted earlier, the total excursion was programmed for 9.22, 1.69, and 1.26 mm (Superior/Inferior, Anterior/Posterior, and Left/Right directions respectively) and taken from the analysis of Seppenwoode (see Table 1).

The 4D CT appear to display uniform Hounsfield numbers for a uniform material. No apparent streaking (artifacts) were generated by the thin aluminum support or the aluminum table. Three orthogonal views of the CT for a single phase of the 4D CT is shown below. The tumor, radiochromic film, sawdust surrogate for lung, Teflon markers are displayed.

There is a sag in the table. Shims correct the tilt and ensured better alignment. There is a surprising sag in the right/left direction (as well as the expected superior/inferior direction). It is probably best to insert shims under the legs of the aluminum support rather than fasten via the screws.

To further verify the positioning of the 3D Linear stage, the center of a Teflon marker was followed in all 10 phases in the 4D CT scan (see below). Superimposed on the positions for the axial, coronal, and sagittal views are the expected positions for the programmed 3D linear stage.

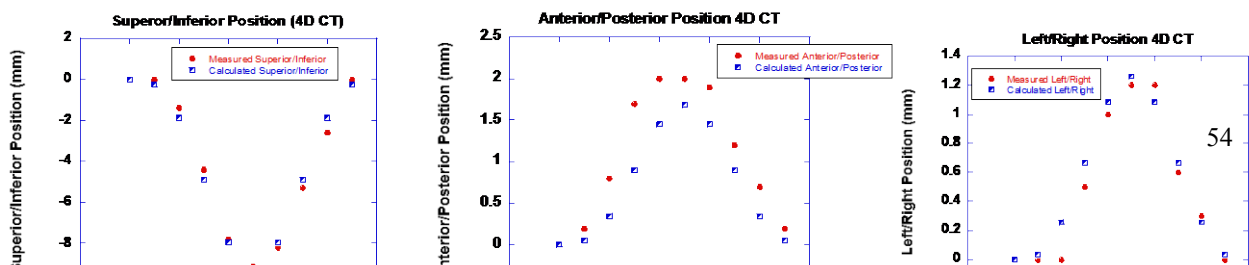


Figure 18 Displacement (mm) and phase for measured and calculated positions for superior/inferior, anterior/posterior, and left/right views

A portion of the anterior side of the thorax phantom was cut to ensure easier filling of the lung cavity with sawdust. Elmer epoxy and gel were used to help reduce the space between the wedge and the rest of the thorax phantom. The Elmer epoxy and gel were scanned and found to have HU respectively.

Photon Treatment Plan Applied to Thorax Phantom and Mobile Tumor

To test the thorax phantom, an ECLIPSE photon plan was generated to treat the mobile tumor undergoing large amplitude motion. An ITV and target structure was generated using the ECLIPSE MIP (Maximum Intensity Projection) feature in ECLIPSE. The ECLIPSE plan used the (time) average CT for planning purposes. Seven beams were used to achieve a uniform dose within the target. The plan invoked the Varian Trilogy machine's 6 MV photons. The number of anterior fields were limited to reduce the effect of the cutout wedge used for filling sawdust into the lung cavity. The beam arrangement and dose distributions are shown for three orthogonal orientations

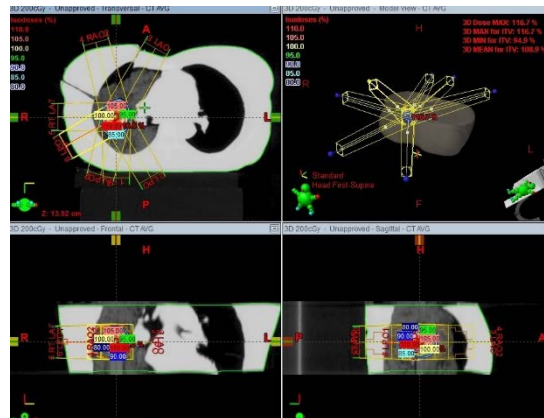


Figure 19 Isodose contours and 7 field treatment plan applied to tumor within thorax phantom undergoing large amplitude motion

Dosimetry for Photons Applied to Thorax Phantom and Mobile Tumor

Radiochromic film will be placed between the tumor hemispheres and supported within the cedar shaft. Photon radiation from Trilogy machine will be deposited onto the phantom, lung surrogate, and tumor undergoing large amplitude motion. The dose will be collected and analyzed using the multichannel dosimetry (Mayer et al. 2012). The dose will be compared to the treatment plan through gamma analysis (Low et al. 1998).

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