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TITLE: Proton Therapy Dose Characterization and Verification

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14. ABSTRACT This report describes the first year of work on the award "Neurocognitive Effects of Radiotherapy". The first year's effort has been in two areas: (1) to get an approved protocol that will be used to study patients via MRI and neurocognitive testing, and (2) to develop immobilization equipment that enables us to deliver base-of-skull treatments more optimally. The study has gotten IRB approval at Penn and recently a DOD approval. A component (10%) of this award supports the work done by the Walter Reed Army Medical Center scientists.					
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a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)

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

Primary Objectives: (1) 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. (2) 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. (3) To relate these imaging characteristics to the degree of memory loss.

Methods: Eligible subjects will include patients with malignancies of the skull base or patients with low grade glioma who require radiotherapy. 10 subjects receiving photon treatment plans and 20 subjects receiving proton treatment plans with malignancies involving the base of skull and a total of 40 patients with low grade glioma 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 at 1.5, 4.5, 12, and 24 months following completion of the radiotherapy for patients with low grade glioma and 1.5 and 12 months post radiotherapy for patients with malignancies involving the skull base. Both cohorts will repeat standard neurocognitive evaluation at 1.5, 4.5, 12 and 24 months following completion of radiotherapy.

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 malignancies, and (2) those with low-grade gliomas.

Progress

The approval process at Penn for the neurocognitive study took most of the first year after which the study was sent for DOD approval. It was approved few months ago. That meant that only in the summer of 2011 we were ready to start enrolling patients. The 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” funded by a grant from the Department of Defense (DOD) Telemedicine and Advanced Technology Research Center (TATRC) has been open for accrual since August of 2011. Its objectives include 1) to estimate the degree of cognitive loss following radiation therapy and 2) to demonstrate evidence of radiation induced subclinical vascular and neuronal injury in adjacent brain regions receiving exit doses of radiation.

To date, we have screened a total of 3 patients and enrolled two patients (both in cohort 2) that are currently active in the study (currently undergoing radiation). They have completed the initial baseline imaging and battery of neurocognitive testing required. We expect to accrue another two patients (into cohort 1) in the next few weeks. In addition, we are actively recruiting normal controls for comparison as well. Patients currently enrolled have responded favorably thus far.

- 1.
2. We did complete the design and construction of a prototype immobilization device for treating patients with base-of-skull (and other brain) cancer. This development adapted an existing product manufactured by WFR-Aquaplast so it would work in our facility. It along with the MLC from phase 1 is pictured below.



Appendix I. Protocol

August 26, 2010

Harry Quon, MD
2 Donner

RE: UPCC 08310: 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

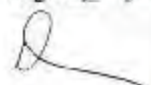
Dear Harry:

Thank you for your response to the CTSRMC stipulation letter for the above-referenced study. I have reviewed your responses along with the protocol amendment version 7/20/10 and consent form version 7/20/10. I find that the changes are acceptable and, therefore, I am granting the study full approval.

CTSRMC Approval may be withdrawn if the following on-going requirements are not met:

1. **Amendments:** Any modifications to the protocol, consent(s) or other study related documents must be submitted electronically to Jane Daly jane@mail.med.upenn.edu. Revisions cannot be initiated until CTSRMC approval has been given.
2. **Accrual Monitoring:** The CTSRMC is mandated by NCI to assess the scientific progress of your study. This is accomplished through monitoring enrollment onto your study every three months from the date your protocol opens to enrollment and evaluation of your annual Continuing Review. Late or inaccurate accrual data prevents the CTSRMC from meeting our obligations to NCI. **As you accrue patients to this study, you must update your accrual information in Velos.** <https://velos.uphs.upenn.edu:5443>
3. **Exceptions/Deviations:** Any variation from the approved protocol must be acted upon appropriately. The IRB and ACC Data and Safety Monitoring Committee have specific documentation and reporting requirements. Please visit their websites to familiarize yourself with their expectations. DSMC requirements can be reviewed at www.ctsrcmc.org
4. **Completion of Study:** Please notify the CTSRMC in a timely manner when the status of your study changes (e.g. closes, terminates, suspended, withdrawn). Inaccurate data prevents the CTSRMC from meeting our obligations to NCI. **You are required to keep your study status current in Velos.** <https://velos.uphs.upenn.edu:5443>

Regards,


Douglas Fraker, MD
Chair, Clinical Trials Scientific Review and Monitoring Committee

cc: IRB
Vicki Sallée, MS, RD

