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14. ABSTRACT
This report describes continued work on the award "Neurocognitive Effects of Radiotherapy", which examines the neurocognitive and imaging impact of proton therapy for patients will low grade glioma and base of skull meningioma. A total of 58 patients have been enrolled. All cohort 1 and 2 patients have completed a 4-5 hour neurocognitive testing assessment at baseline by Dr. Carol Armstrong. In addition, cohort patients have completed a 1 hour standard MRI as well as additional testing including diffuse tensor imaging (DTI), perfusion and diffusion. Thirty-four patients have completed neurocognitive and imaging evaluation at planned timepoints.
Dr. Michelle Alonso-Basanta is Principle Investigator for this. Catherine Feinstein is the Clinical Research Coordinator managing the associated IRB-approved protocol. Dr. Christine Hill-Kayser is the Project Manager for this section of the award. Further budgetary details are outlined in the attached document.

15. SUBJECT TERMS
Radiation Oncology, Proton Therapy, Image-Guided Radiotherapy, Neurocognitive, MRI

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1. 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.

2. KEYWORDS:

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

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

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.

Timeline set included:

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

Summary of Goals:

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.

Therefore, the primary objectives **of this phase 6 were:**

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.

-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.

-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 as measured by prospective, longitudinal neurocognitive testing.

Secondary objectives were:

-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.

Schema Design is below:

	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

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the

project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

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 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. A total of 58 patients have been enrolled; 24 normal cohorts and 34 patients for cohorts 1 and 2 (31 protons and 3 photons).

The table attached includes all study procedures that have been completed as of 10/1/2017. Dates at each time point (per patient) include having completed neurocognitive testing assessment (by Dr. Carol Armstrong and her team) as well as MRI scans (standard MRI as well as diffuse tensor imaging (DTI), perfusion and diffusion).

Table 1.

Initials	Sex	Age	Study ID	Consent	EOT	Baseline	#1 ~1.5M	#2 ~6 M	#3 ~12 M	#4 ~24 M	Comments
2011 / 2 females											
SXG	F	37	C2-001	9/14/2011	11/25/2011	10/3/2011	1/26/2012	4/5/2012	12/10/2012	1/13/2014	LGG
MXD	F	62	C2-002	10/11/2011	12/16/2011	11/2/2011	1/23/2012	6/4/2012	4/16/2012	12/16/2013	LGG
2012 / 4 females, 2 males											
BXJ	F	48	C2-003	1/21/2012	3/13/2012	1/24/2012	4/17/2012	9/8/2012	5/3/2013	9/26/2014	BOS Meningioma
SBM	F	37	C2-004	5/16/2012	7/18/2012	6/4/2012	9/12/2012	1/28/2013	7/22/2013	8/4/2014	LGG
ALR	F	32	C1-001	6/19/2012	8/21/2012	7/3/2012	missed	4/19/2013	8/27/2013	8/25/2014	BOS-Schwannoma
SXM	M	31	C1-012	6/19/2012	9/12/2012	7/13/2012	missed	2/18/2013	9/16/2013	10/13/2014	BOS-Chondro
FAC	F	35	C1-011	6/20/2012	8/21/2012	7/3/2012	11/15/2012	2/7/2013	7/29/2013	7/22/2014	BOS-Pituitary
ORO	M	27	C1-013	9/17/2012	11/5/2012	9/19/2012	2/25/2013	5/20/2013	9/13/2013	*2/9/2015*	BOS-Chordoma
2013 / 6 females, 2 males											
SXZ	F	46	C1-002	2/8/2013	3/25/2013	2/8/2013	4/22/2013	9/17/2013	5/19/2014	3/20/2015	BOS-Pituitary
AXG	M	21	C1-014	2/15/2013	4/15/2013	2/28/2013	5/14/2013	10/18/2013	5/20/2014	M: 5/20/15 T: 5/21/15	BOS-Pituitary
RXW	F	57	C1-015	4/11/2013	6/20/2013	4/23/2013	7/23/2013	12/12/2013	6/17/2014	7/6/2015	BOS-Chondro
NXP	F	28	C2-005	5/29/2013	8/5/2013	6/18/2013	9/19/13 test 10/3/13 MRI	missed	8/6/2014	MISSED	Meningioma
JAC	F	55	C1-016	8/15/2013	9/26/2013	8/15/2013	11/14/13test 11/15/13MRI	3/21/2014	10/6/2014	10/5/2015	BOS-Schwan
2013 cont											
KXS	F	32	C2-006	11/20/2013	1/28/2014	12/3/2013	3/24/2014	MISSED	*2/16/2015*	2/22/2016	LGG
KXV	M	27	C2-007	12/4/2013	2/25/2014	1/10/2014	WITHDRAWN				LGG
LXF	F	35	C1-017	12/18/2013	3/3/2014	1/6/14test 1/20/14MRI	5/30/2014	10/29/2014	Missed	3/29/2016	BOS-Meningioma

2014 / 9 females, 3 males

PXM	M	26	C2-008	1/29/2014	4/14/2014	2/24/2014	6/3/2014	10/14/2014	DRAWN 4/24/2015		Meningioma
DXP	F	48	C2-009	3/5/2014	5/5/2014	3/19/2014	6/24/2014	MISSED	MISSED	7/25/2016	LGG
EPM	F	55	C1-018	3/10/2014	4/28/2014	3/10/2014	6/9/2014	12/1/2014	4/8/2015	M: 4/4/16 T: 5/4/2016	BOS-LGG
MXH	F	46	C1-019	4/11/2014	5/29/2014	4/11/14MRI 4/16/14test	7/28/2014	M 12/30/14 T 1/9/15	6/16/2015	7/12/2016	BOS-Meningioma
RXJ	F	48	C1-020	4/15/2014	6/5/2014	4/15/2014	7/30/2014	1/13/2015	6/9/2015	7/26/2016	BOS-Pituitary
AXH	M	54	C1-021	4/14/2014	5/22/2014	4/14/2014	8/27/2014	T:12/10/14 M:12/18/14	5/14/2015	10/25/2016	BOS-Pituitary
CXB	F	39	C1-022	4/16/2014	6/16/2014	4/22/2014	7/29/2014	M:12/9/14 T:12/22/14	6/9/2015	6/7/2016	BOS-Meningioma
ERM	F	27	C1-23	7/2/2014	9/5/2014	7/16/2014	10/28/2014	*2/25/2015 MRI 3/2/2014 TEST*	10/15/2015	11/30/2016	BOS-Pituitary
KDW	F	26	C2-010	8/25/2014	10/22/2014	9/3/2014	9/11/2014	5/19/2015	12/1/2015	12/13/2016	LGG
LXM	F	64	C1-24	10/13/2014	12/1/2014	10/13/2014	1/12/2015	6/8/2015	12/7/2015	T 12/5/2016; M 12/6/16	

2014 cont

PMM	F	57	C1-25	11/4/2014	1/8/2015	11/12/2014	*2/9/2015 MRI 2/15/2015 TEST*	7/7/2015	1/18/2016	1/16/17 MRI, 1/23/17 T	
SXA	M	53	C1-26	12/18/2014	3/12/2015	1/5/2014	M: 4/27/15 T: 4/29/15	MISSED	3/7/2016	3/6/2017	

2015 / 3 females, 3 males

BXG	F	45	C1-027	1/28/2015	4/22/2015	2/4/2015	6/19/15 test; 6/22/15 MRI	12/17/2015	'18/16 T; 4/1	4/12/2017	BOS-Meningioma
RMR	M	73	C1-003	4/13/2015	6/18/2015	4/13/15 Test, 4/16/15 MRI	8/13/2015	12/28/2015	/28/16 , T:7/	6/13/2017	BOS-Meningioma
RRL	M	66	C1-028	5/20/2015	7/20/2015	5/20/2015	M:10/27/15; T:10/28/15	1/19/2016	7/19/2016	8/1/2017	BOS-Solitary Fibrous Tumor
TXA	F	29	C1-029	5/27/2015	8/25/2015	6/10/15 Test; 6/12/15 MRI	Missed	3/21/2016	Missed	10/17/2017	BOS-Chordoma
MXR	M	36	C1-030	6/18/2015	8/4/2015	6/18/2015	9/11/2015	2/8/2016	8/2/2016	7/18/2017	BOS-Pituitary
SXW	F	56	C2-011	7/14/2015	8/31/2015	7/14/2015	12/3/2015	T:03/29/16 M: 5/24/16	9/28/2016	8/15/2017	BOS-glomus jugulare

A preliminary clinical brief report is currently underway. Here is a summary of our findings thus far:

Adults age 18 – 70 with primary brain tumors were recruited from 2011 to 2015. Patients were referred by Neuro-Oncology conferences at the University of Pennsylvania, and investigations were performed after approval by the Institutional Review Board of the Hospital. Of 34 eligible patients, 31 were treated with proton therapy or a combination of proton and photon therapy. Of the 31 patients enrolled, 8 (26%) were female, 19 (61%) had a college degree or advanced degree, 25 and (81%) identified as white. Tumors were meningiomas (32%), gliomas (26%), pituitary adenomas (13%), and other (29%).

Historical Controls

Patients in this study were compared to a set of historical controls previously published. Of these 70 historical patients with low-grade, supratentorial brain tumors, 41 received photon radiation and 29 had no radiation therapy. They had a similar battery of neuropsychological testing at baseline and annually for two years following radiation, resection, or diagnosis depending on treatments received. Of these patients, 51% were female and median education was 16 years. Tumors were gliomas (65%), neuroendocrine tumors (15%), meningiomas (12%), and other (9%).

Treatment

Patients received proton radiation to a median of 54 Gy (IQR 54 – 59 Gy) in 180 cGy per fraction. Targets were in the Base of Skull (61%), Frontal Lobe (19%), Temporal Lobe (13%), and Parietal Lobe (6%) with a median Gross Target Volume of 31.3 cc (IQR 7.9 – 44.7 cc). Of the 31 patients receiving proton therapy, 8 (26%) received a combination of proton and photon therapy.

Table 2. Demographics

Gender	
Female	71%
Male	29%
Profession	
Education	21%
Business & Management	21%
Sales	9%
Other	50%
Educational Attainment	
College Degree or higher	57%
Did Not Finish High School	7%
Ethnicity	
White	79%
Asian	6%
Black	3%
Other	12%
Family History	
Cancer	74%
Psych or Neuro Disorder	9%

Table 3. Clinical Information

Histology		
Meningioma	32%	(11)
Glioma	24%	(8)
Pituitary Adenoma	15%	(5)
Other	29%	(10)
Location		
Base of Skull	65%	(22)
Frontal	18%	(6)
Temporal	12%	(4)
Parietal	6%	(2)
Treatment		
Proton Only	67%	(23)
Photon Only	10%	(3)
Proton and Photon	23%	(8)
Steroids	29%	(10)
AEDs	29%	(10)

Psychiatric Medications	22%	(7)
Functional Status		
ECOG 0	39%	(13)
ECOG 1	58%	(20)
ECOG 2	3%	(1)
Radiation Thearpy		
Median Dose	55 Gy	(37 - 78 Gy)
Median GTV	15.6 cc	(0.1 - 127.6 cc)
Fraction Size	180 cGy	
Acute Toxicities Grade 2 or Higher		
Fatigue	36%	(11)
Insomnia	15%	(5)
Headache	12%	(4)
Cognitive Disturbance	6%	(2)

Results

Local Control and Overall Survival

Median time of follow-up was 24 months. Local control and overall survival were 100% at 2 years. At 2 year follow-up, 16% of patients had a partial response to radiotherapy and 84% showed stable disease. Progression free survival was 100% at 2 years.

Acute and Delayed Toxicity

The treatment was well-tolerated acutely. Only one patient had Grade 3 toxicity of headaches. Notably 91% of patients experienced some amount of fatigue and 61% had some amount of headaches. Additionally, at the end of treatment visit, 39% had Grade 1 alopecia or nausea, 36% had Grade 1 dysphasia, and 33% developed Grade 1 dermatitis. In follow-up, three patients had Grade 3 toxicity of anorexia, vision changes, or seizures. None had worse than Grade 3 toxicity. In long term follow-up, 66% of patients continued to have fatigue, while 44% had headaches. Though 35% of patients had at least Grade 1 vision changes, at baseline 41% of patients already had vision changes prior to radiation. Similarly, several patients showed improvements of paresthesia, dysphasia, depression, and insomnia in follow-up.

Table 4.

Acute Toxicity	**Grade 1**	**Grade 2**
Alopecia	39%	
Dermatitis	33%	
Nausea	39%	
Constipation	24%	
Depression	30%	
Insomnia	24%	15%

Paresthesia	21%		
Dysphasia	36%		
Headache	48%	9%	3%
Cog Disturbance	18%	6%	
Anorexia	24%		
Fatigue	55%	36%	

Table 5.

Acute Toxicities Grade 2 or Higher	
Fatigue	36% (11)
Cognitive Disturbance	6% (2)
Headache	12% (4)
Insomnia	15% (5)

Table 6.

Follow-Up Toxicity		Baseline Toxicity	Change from Baseline***
Grade 3			
Anorexia	3%	0%	3%
Seizure	3%	0% (3% had Grade 2)	3%
Vision Changes	3%	3%	0%
Grade 2			
Fatigue	16%	6%	10%
Paresthesia	11%	3%	8%
Headache	9%	0%	9%
Alopecia	6%	0%	6%
Cognitive Distur	5%	6%	-1%
Insomnia	5%	6%	-1%
Depression	5%	6%	-1%
Vision Changes	3%	0%	3%
Facial Weaknes	3%	3%	0%
Other Weaknes:	3%	6%	-3%
Ataxia	3%	3%	0%
High Frequency Toxicities (any grade)			
Fatigue	66%	62%	4%
Headache	44%	53%	-9%
Vision Changes	35%	41%	-6%
Paresthesia	33%	38%	-5%
Dysphasia	26%	29%	-3%
Cog Disturbanc	25%	23%	2%
Depression	23%	26%	-3%
Insomnia	21%	30%	-9%
Hearing Change	21%	9%	12%
Other Weaknes:	20%	18%	2%

***Red - Increase in toxicity; Green - Decrease

Neurocognitive Effects

We adapted for this study four experimental tests of cognition that were found in prior studies to demonstrate activation in the cerebellum. In order to apply the tests that we proposed are cerebellar-sensitive, and to determine if they are useful cognitive markers of radiation injury, the tests should be stable in healthy controls over two time points. The cognitive markers reported in the progress note of 2014 (Timing Functions, Serial Response, and Audiovisual Attentional Shift) included several indices that demonstrated stability across two time points in healthy controls (N=25) who were similar to patients (N=33) in age (p=0.40) and education (p=0.15).

Applying a Bonferroni correction to paired t-tests, one of the 40 cerebellar test indices met criterion for significant difference between the two time points in the healthy controls, due to a small practice effect. Other tests not meeting the error criterion but showing a trend demonstrated the same pattern of slightly better performance at the second test time. It is not unexpected that some practice effect would be found as the implicit cognitive system is very robust and can be functional even in the presence of cortical disease. The results over two test

sessions indicate that the tests are reliable, and further analyses are needed to examine their role in measuring possibly declines following proton therapy in patients with brain tumors.

Effects over Two Years in the Cognitive Markers of Radiation Injury

Complete data from baseline to two years was analyzed in a mixed model in 31 patients who received Proton therapy (PRT) and 45 brain tumor patients who received photon radiotherapy (XRT) from a historical dataset. The effects were examined before Protons and at three time points after Protons to two years, using a mixed effects model that included interval, therapy type, and individual random effects. Measures were tested for significance using chi-square and z-statistics corresponding to the time-by-treatment interaction arising from mixed-models regression. We hypothesized that tests of verbal semantic memory would be sensitive to PRT, and that visual-perceptual memory would be insensitive to PRT. The hypotheses were confirmed: only the tests of retrieval of words from long-term memory (and not learning of the words) and the reaction time to retrieve semantic pictures (and not recall of perceptual figures) demonstrated the decline and recovery that were seen in patients who received XRT (Figure below).

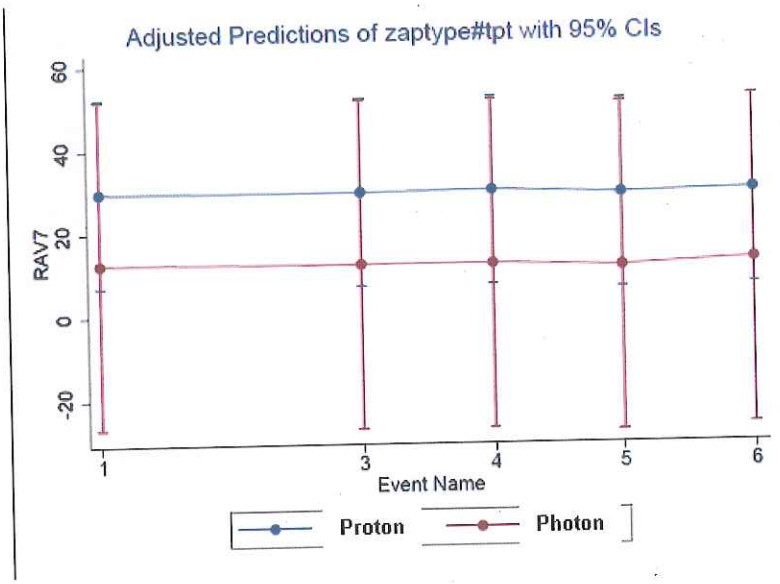


Figure 1: Blue = PROTON; Red = PHOTON; 1 = pre-XRT; 3=1.5m post completion of RT, 4 = 6 m post baseline, 5 = 1 y post baseline, 6 = 2 y post baseline

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

Patients receiving PRT had significantly (or trending) stronger cognitive scores in most of the test indices at baseline and throughout the two years of the study. In particular, there was a trend to significance towards improved mini-mental status scores (not done in the historical controls) in the proton therapy group over time.

In reviewing the cognitive data for both cohorts together, there is still a tremendous amount of work to be done in regards to appreciable changes noted by testing. We did not find that all parameters were significantly different when compared to historical controls and will now

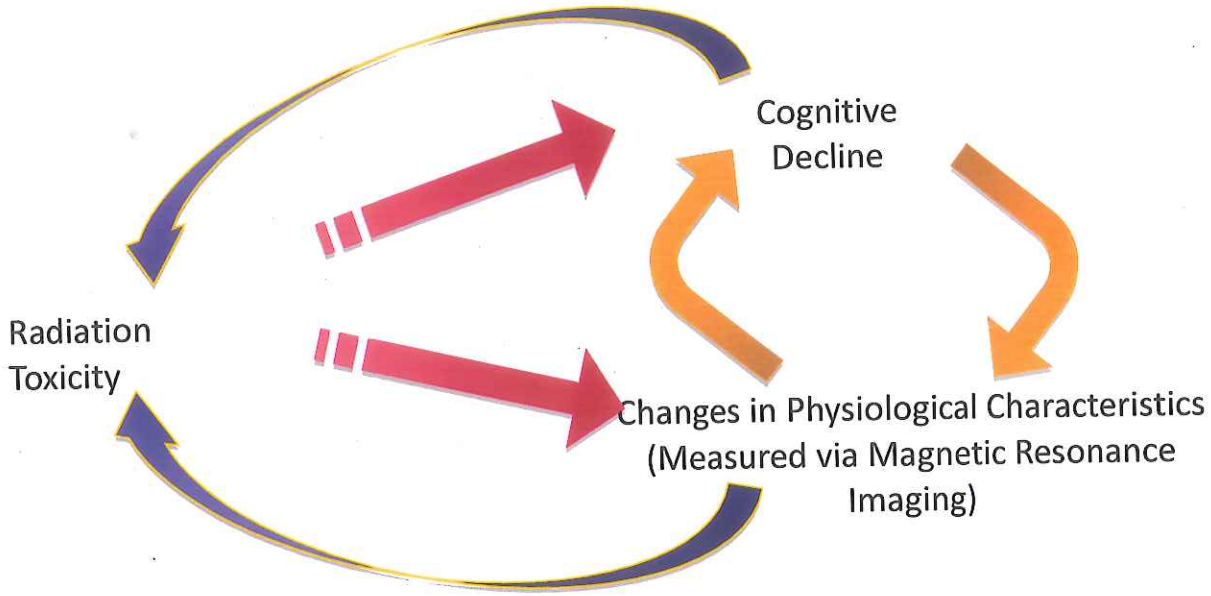
review and breakdown more distinctly the two cohorts as they relate to location. In particular, we will be reviewing the role of radiation to the cerebellum as it relates to these scores. More is due in this regard.

MRI Evaluation: Preliminary Results

MRI evaluation was started in 2015/2016 with a great amount of work done on consolidating data in one database system for ease of use amongst both radiology and radiation oncology. Due to the need for neurocognitive evaluation to be complete in order to correlate some changes noted, and given this was a secondary objective of the study, this will be the work of our colleagues in the department of radiology and radiation oncology for FY19 and 20. We are attempting to obtain funding for a lead researcher with imaging interest and background to assist with this once it is all compiled. Below is what we have thus far.

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

Figure 2



There are various parameters that can be measured with MRI and will briefly be described. As the signal is given off by relaxation of the excited protons in the body, we can obtain the diffusion tensor imaging (DTI) which includes parameters such as the Apparent Diffusion Coefficient (ADC) or the Fractional Anisotropy (FA). ADC is the mean diffusion outwards from a relative point and describes the cellular density of that voxel. The FA gives us unidirectional diffusion and allows us to measure the directional component of the diffusion. Alternatively, we can also obtain the Dynamic Susceptibility Contrast (DSC) which allows us to measure the Relative Cerebral Blood Volume (rCBV). This describes the blood volume in a region of interest and is an indicator of vascularization (or lack there-of) relative to white matter.

MRI images were collected before radiation treatment (baseline), and approximately 1.5, 6, 12, and 24 months after the completion of radiation therapy (RT). During a MRI study session, 19 pulse sequences were conducted, generating T1-weighted, T2-weighted, FLAIR, diffusion-tensor-imaging (DTI), permeability, perfusion, and spectroscopic images. In general, MRI studies were performed on the same day of the cognitive testing, and took an hour to finish.

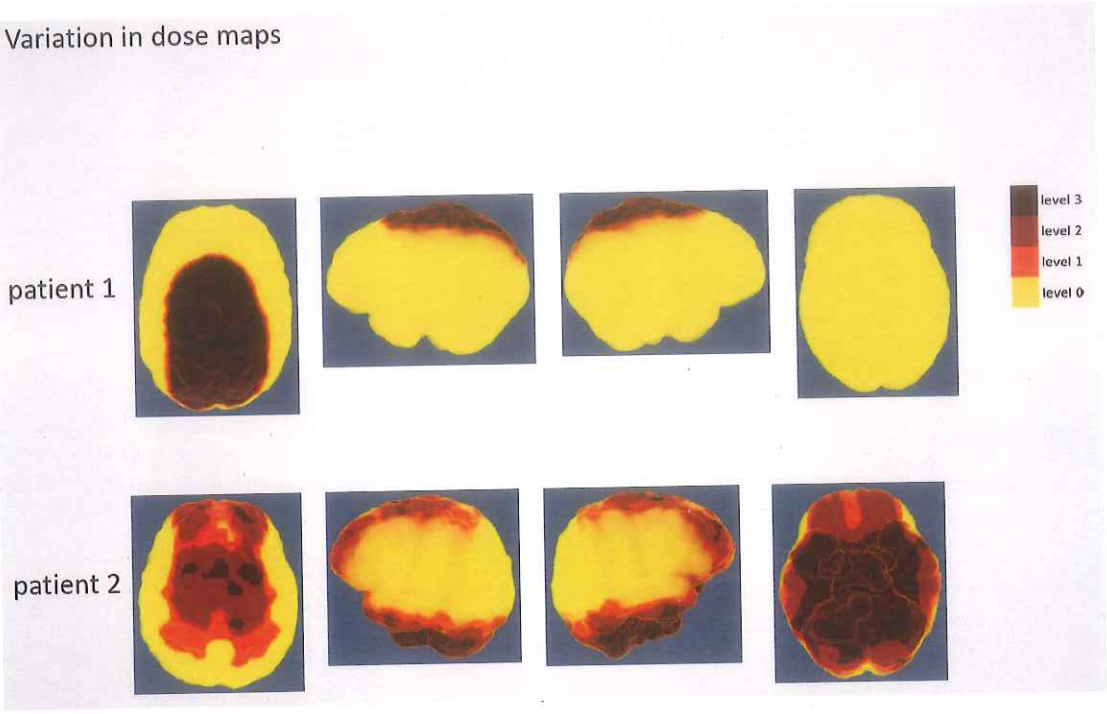
In 2015, we continued to scan new patients, and completed MR-parameter extraction of regions of interest (ROI), i.e., structural contours, for the eight patients who completed the 24 months follow-up neurocognitive study. Specifically, MRI data were first co-registered with one another, and then structurally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

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

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

In 2016, we have collaborated with additional colleagues in radiology to review and examine our unique data set to establish "connectomes" of the brain. Based on research that views the brain as a large inter-connected network, tumor connectome (representation of the brain network in the presence of a tumor) can be created and developed to interrogate the diffusion-based tumor connectome and connectomic measures that will quantify the vulnerability of the brain network in the presence of tumor, based on the functional network that is affected. These maps will be applied to characterize the connectivity changes as the brain recovers post-surgery and after radiation treatment. In conjunction with our current colleagues in radiology who will look at structural changes, this team examines the global effect of radiation on the brain correlating maps to treatment. Figure 3 notes the radiation maps overlay for two example patients.

Figure 3



In review of our early 8 patients that had completed all 5 time points, you can see that there is little local change in connectivity however over time for 4 such patients (Figure 4), however this is a global change noted when compared to radiation dose both in efficiency (Figure 5a) as well as modularity (Figure 5b).

Figure 4

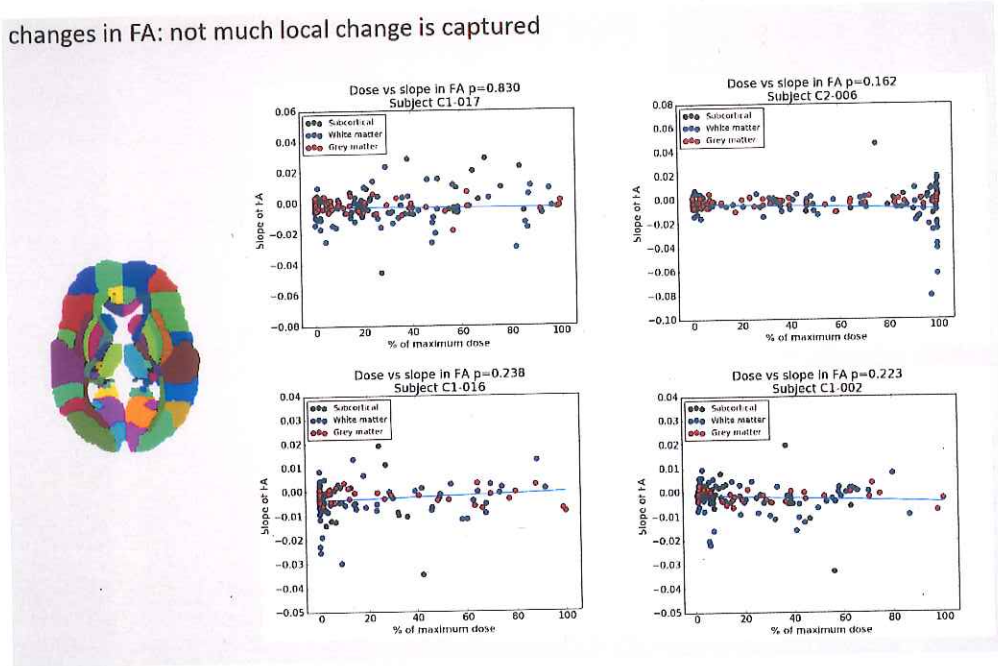


Figure 5a

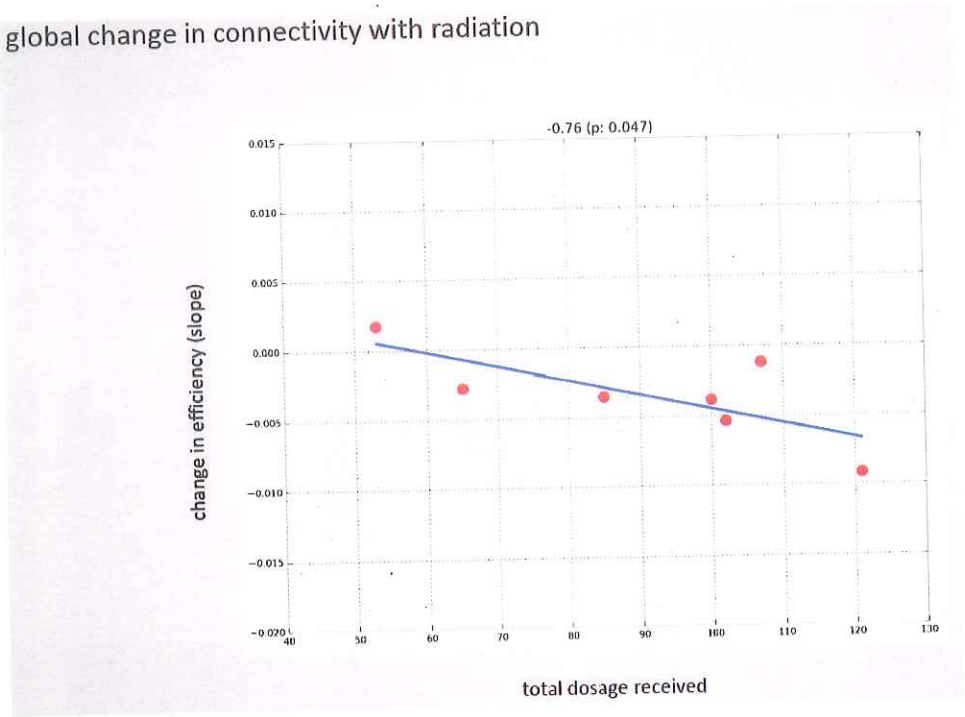
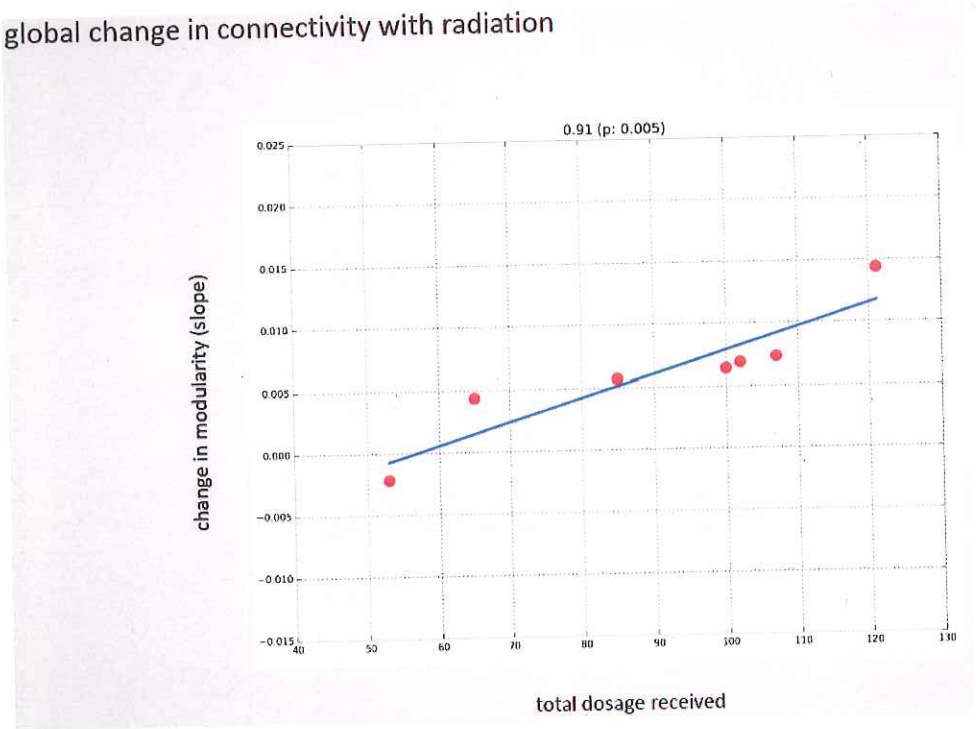


Figure 5b



Additional work is underway to include more data points, as well as establish the temporal correlation of connectivity measures to cognitive scores. The "heat-map" of connectivity changes in the brain after surgery and radiation can then be developed to determine which

pathways are most affected. These maps will then be interpreted as they relate to FA changes we have previously seen. We are excited to see where this will lead in regards to our patients. Neurocognitive data will also be needed to then correlate with the changes noted.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

This project has involved over 20 members of the departments of Radiation Oncology, Radiology, Biostatistics, Neuropsychiatry and Physics. We have had students that have participated in the NIH sponsored SUPERS program at PENN work on this during their summer with us. They have gone on to apply to MD/PhD programs and spurred their interest in neuroscience research. It has fostered collaborations within these departments that were not expected at its concept in 2009. I will say that it will likely continue to provide professional development and exposure as data and analysis leads to publications and invited talks on these topics for all members associated.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

At this time, a brief clinical report (in preparation) is being prepared for submission to a radiation oncology journal. We expect that more publications will be forthcoming once further analysis is done. The publications thus far done are those associated with the early phases of the project and are included below:

1. Fiducial markers in prostate for kV imaging: quantification of visibility and optimization of imaging conditions. Chen Y, O'Connell JJ, Ko CJ, Mayer RR, Belard A, McDonough JE. Phys Med Biol. 2012 Jan 7;57(1):155-72. doi: 10.1088/0031-9155/57/1/155. Epub 2011 Nov 30. PMID:22127351

2. Improving proton therapy accessibility through seamless electronic integration of remote treatment planning sites. Belard A, Dolney D, Zelig T, McDonough J, O'Connell J. Telemed J E Health. 2011 Jun;17(5):370-5. doi: 10.1089/tmj.2010.0199. Epub 2011 Apr 14. PMID: 21492029

Neurocognitive analysis is still at its preliminary stages with then incorporation of relationships to clinical outcome and imaging parameters. This work is ongoing.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

In a clinical sense, the conclusions established will define and support the use of proton therapy for patients with primary brain tumors over the use of photon therapy. Data has already shown that there is no decline in progression free survival or overall survival. These patients had minimal short term or long term side effects. This data will establish that quality of life – how you think and behave – in the longer term will be just as important as that we have control of disease. There are a number of other institutions that have attempted to do this study and have failed due to compliance. We have shown it can be done.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

As mentioned above already, there are a number of collaborations that were not intended at conception that continue to this day. We have not yet met our final primary and secondary objectives for the study however I will say that without the appropriate funding a that crucial time, this group of investigators may not have interacted for this purpose. Instead, it has fostered new investigations that will propagate over time.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

For this phase of the study, there is nothing to report.
However earlier work that was done (see appendix for published work) noted the transfer of data and use of MLCs for proton therapy. This was done in collaboration with our industry partners as well as with collaboration from Walter Reed Medical Center.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

The largest impact on society will be on policy regarding insurance practice and coverage. In the current age, it is not possible to conduct Phase III studies required by insurance companies to prove "benefit". More importantly, the benefit they are seeking is in relation to tumor control and survival. As discussed previously, more impactful is the quality of life for these patients who will now live much longer than their predecessors and who will remain an integral part of society. It is of benefit to such society then that they be able to work, live on their own and be self-sustaining. Many of these patients treated in the past then went on to live with family as they could not afford to live on their own as they were unable to hold down jobs. Most of these same patients then apply to federally funded programs for their welfare and care, adding to the burden nationwide.
Insurance will consider well thought out studies with comparison groups to note the benefits over time in not only control but quality of life.

5. **CHANGES/PROBLEMS:** The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.
Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

During the course of the study, the principal investigator transitioned only once. Early hurdles included

At this time, we will need further work on analysis for the neurocognitive testing although that group is currently at work on this. Our MRI data will require a dedicated researcher to coordinate the various projects that have stemmed from this including analysis comparison anatomically, functionally and globally. This is in addition to the vascular comparison for these patients.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

3. Fiducial markers in prostate for kV imaging: quantification of visibility and optimization of imaging conditions. Chen Y, O'Connell JJ, Ko CJ, Mayer RR, Belard A, McDonough JE. Phys Med Biol. 2012 Jan 7;57(1):155-72. doi: 10.1088/0031-9155/57/1/155. Epub 2011 Nov 30. PMID:22127351

4. Improving proton therapy accessibility through seamless electronic integration of remote treatment planning sites. Belard A, Dolney D, Zelig T, McDonough J, O'Connell J. Telemed J E Health. 2011 Jun;17(5):370-5. doi: 10.1089/tmj.2010.0199. Epub 2011 Apr 14. PMID: 21492029

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to report.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report.

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Databases used are already well established (REDCap).

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

No change from prior.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Walter Reed Medical Center was involved in the early phases of the project. They were not involved in Phase 6.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI

and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. **APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

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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** tumor*s* (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 injury[5]. 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 inflammation [6].

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 al[19] 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 from1986 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 al [20]l, 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) 22845[21]. 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 al[22]. 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 al[23] 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 then 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 al[25] 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 al[13] 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 al[26] 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 Kibert[25] 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 evaluations [4]. 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 Gy [3]. 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 treatment [4]. In contrast, in the group receiving 60-70 Gy for paranasal sinus carcinomas, patient performance was significantly below that expected with tests of memory function [3]. 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	Standard of	X	X	X	X	X

Skull (n=30)	Care MRI					
	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 1.72x1.72x3mm^3, 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 cm^2, 3mm slice thickness, 128 x 128 matrix, b values = 0 and 1000 s/mm^2 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 = (□□□□□□□□□□□□□□□□□□□□

(1)

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

MRS:

Single slice 2D multivoxel ^{1}H MRSI will be performed using a spin echo sequence with water suppression using a TR/TE = 1700/30ms, NEX = 3, field of view =16x16 cm^2, 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 ^{1}H MRSI spectra will be acquired and the unsuppressed water signal will be used for computing metabolite concentrations.

MRS Data Analysis

All ^{1}H 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 inputs[29];

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 sequence [32];
8. Semantic Fluency Test (Animals);

Executive and Conceptual Processes:

9. Balls in a Bottle Test – an inferential reasoning task[33],
10. Timing Functions T. – perception of time intervals [34];
11. Trails B
12. Phonemic Fluency Test

Visuomotor Scanning Speed:

13. Trails A

Mood, fatigue:

14. Fatigue Severity Scale[35],
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 $4000/mm^3$, platelets greater than or equal to 100,000 mm^3 and Creatine 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/mm^3, platelets greater than or equal to 100,000 mm^3 and Creatinine 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 $\pm$ 3.54 words (SD^2 = 12.53). Data for each group at each time point were:

		Months from the completion of radiation		
Observed values	baseline	1.5	6	12
Mean # words	10.20	8.45	9.53	10.69
Radiation				
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.

	Months from the completion of radiation			
Expected values	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 and 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 – II - Publications

Improving Proton Therapy Accessibility Through Seamless Electronic Integration of Remote Treatment Planning Sites

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Abstract

Objectives: *Proton radiotherapy is a relatively scarce treatment modality in radiation oncology, with only nine centers currently operating in the United States. Funded by Public Law 107-248, the University of Pennsylvania and the Walter Reed Army Medical Center have developed a remote proton radiation therapy solution with the goals of improving access to proton radiation therapy for Department of Defense (DoD) beneficiaries while minimizing treatment delays and time spent away from home/work (time savings of up to 3 weeks per patient).* ***Materials and Methods:*** *To meet both Health Insurance Portability and Accountability Act guidelines and the more stringent security restrictions imposed by the DoD, our program developed a hybrid remote proton radiation therapy solution merging a CITRIX server with a Joint Interoperability Test Command (JITC)-certified desktop videoconferencing unit. This conduit, thoroughly tested over a period of 6 months, integrates both institutions' radiation oncology treatment planning infrastructures into a single entity for DoD patients' treatment planning and delivery.* ***Results:*** *This telemedicine solution enables DoD radiation oncologists and medical physicists the ability to (1) remotely access a proton therapy treatment planning platform, (2) transfer patient plans securely to the University of Pennsylvania patient database, and (3) initiate ad-hoc point-to-point and multipoint videoconferences to dynamically optimize and validate treatment plans.* ***Conclusions:*** *Our robust and secure remote treatment planning solution grants DoD patients not only access to a state-of-the-art treatment modality, but also participation in the treatment planning process by Walter Reed Army Medical Center radiation oncologists and medical physicists. This telemedicine system has the potential to lead to a greater integration of military treatment facilities and/or satellite clinics into regional proton therapy centers.*

Key words: *cancer, radiation therapy, virtual medical simulation, remote treatment planning*

Introduction

According to the National Center for Health Statistics, one in four deaths in the United States is due to cancer.[1] In the arsenal of treatment modalities used to manage the disease, proton radiation therapy is a relatively new weapon. Because the technology involved in producing and delivering protons is quite complex, the cost of developing multiroom proton therapy centers is significant (anywhere between $150 and $250 million dollars depending on the number of gantries deployed). At the time of writing this article, there were only nine centers in the United States offering comprehensive proton radiotherapy.

Through public law, a partnership was established in 2004 between the hospital at the University of Pennsylvania (UPenn) (Roberts Proton Therapy Center) and the Walter Reed Army Medical Center (WRAMC) (Department of Radiology–Radiation Oncology Service) to engage in several areas of research as it pertains to the delivery of proton radiation therapy. One of the goals of this grant was the development of a robust remote proton radiotherapy treatment planning system to (1) facilitate the determination of protocol eligibility and enrollment at the local level, (2) eliminate duplicate consultations by different radiation oncologists, duplicate tumor board reviews, and duplicate image staging, and (3) significantly reduce the patient's time away from work and family by performing the entire treatment planning process remotely (i.e., simulation, fabrication of immobilization devices, contouring, plan creation, dose calculation, and plan approval and prescription). Although the field of radiation oncology has used telemedicine in the recent past,[2–6,34] and more specifically, as it applies to both Department of Defense (DoD) and Veterans Affairs beneficiaries,[7,8] we believe our solution pushes a new frontier.

Materials and Methods

Building upon our experience with the "Remote Proton Radiation Therapy over Internet2" prototype,[9] our research program has developed a hybrid telemedicine solution that offers the following functionalities to the remote cancer-care provider: (1) ability to conduct both planned or ad-hoc high-definition audio-videoconferences with one or more sites, (2) ability to upload treatment plans to a shared folder via a secure virtual private network (VPN) connection, (3) sharing of treatment planning applications with authorized users for the purpose of optimizing/validating prescriptions, and (4) seamless integration of the hybrid design with existing multipoint control units (MCU) for calls involving more than two sites.

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This hybrid solution merges a high-definition video teleconferencing (VTC) unit configured over an integrated services digital network (ISDN),[10,11] with an internet protocol (IP)[12] CITRIX client. Before selecting a desktop VTC unit, our research program looked at all available models from both Polycom and Tandberg. Demonstrations at the American Telemedicine Association Annual Meeting (Nashville, 2007 and Seattle, 2008) and in-house (Directorate of Information Management) confirmed that all units would meet our requirements in terms of connectivity (IP) and quality (minimum of 640 by 480 pixels). Our engineers seemed to have a slight preference for the Tandberg models, for both their Joint Interoperability Test Command (JITC) certification and their substantial use within the DoD network. Once confronted with the option of going either SD (standard definition or 480i max resolution) or HD (high definition or 1080i/720p max resolution), we opted for the latter, anticipating that future improvements in network capabilities would result in improved visual content for the users.

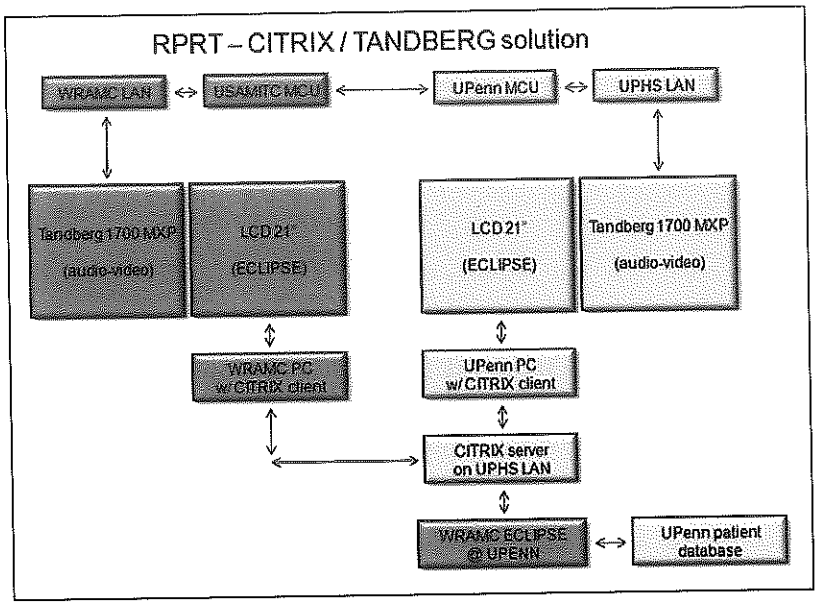

Fig. 1. Schematics of the hybrid solution (part 1).

Our choice was the Tandberg 1700 MXP, a 20-inch widescreen LCD with a high-definition audio-videoconferencing unit equipped with a built-in HD camera. Of the four units we initially purchased, two had the embedded multisite functionality, thus turning them into a portable MCU for up to four sites. The Tandberg further gave the ability to place calls up to 2 megabits-per-second with H.235 encryption. With true CD-quality audio, protection against network interruptions for point-to-point calls, and superior video quality (H.264 standard), the 1700 MXP seemed like a very robust desktop HD VTC solution. Finally, the 1700 could also serve as a PC monitor, thus doubling the virtual workspace of physicians.

Three of these hardware codecs were initially purchased for evaluation, at a cost of $8,000 per unit. Two were placed at the WRAMC (Radiation Oncology Service) and one at the UPenn (Department of Radiation Oncology). The three units were configured over their respective networks (MEDNET and UPHS).

For the two Walter Reed units, connectivity was achieved via an IP connection from the endpoint itself to a Tandberg Codian gateway. Both were assigned phone numbers by the United States Army Medical Information Technology Center (USAMITC); calls placed from these units are therefore IP pre-gateway and ISDN post-gateway. UPenn is using a similar setup at their end, having their endpoint connected via IP to their Polycom RMX 2000 bridge and also registered with their gatekeeper/gateway for ISDN calls.

Our current setup (*Figs. 1* and *2*) pairs a Tandberg 1700 MXP with a standard 21-inch flat-screen liquid crystal display linked to a clinical computer. For its application-sharing function, our research program initially selected Defense Connect Online (DCO), an Adobe Connect product developed for the DoD. We tested both the DoD version and the commercial version of the core product. Both of those allowed us to evaluate window management (note, chat, attendee list, camera, share), as well as application sharing. DCO, based on the professional version of Adobe Connect, also offered additional functionalities, but those were of no particular benefit to our program (meeting recordings, administration and reporting, large events and polling, etc.).

Although free, DCO came with several drawbacks: (1) only individuals affiliated with the DoD can create an account and therefore open a room for data collaboration and (2) calls have the potential to be recorded and subsequently reviewed by staff who did not receive Health Insurance Portability and Accountability Act (HIPAA) certification. Because the risk of compromising a patient's protected health information was very real, our program decided to abandon this platform to focus instead on a CITRIX client for both the secure transfer of patient files and the sharing of the treatment planning application.

CITRIX is a powerful application granting users not only the ability to transfer files securely from their local workstation to a remote site, but also take control of an application remotely. In addition, the "shadowing" function allows the far user to also take part in any remote session, thus offering the ability to collaborate dynamically in real time. CITRIX is not only endorsed by the DoD, but also certified to meet all current HIPAA requirements. The application being accessed via CITRIX is an Eclipse treatment planning platform (Varian Medical Systems), enabled for both photon and proton calculations.

A CITRIX server was purchased by the research program and subsequently configured on the UPHS network; 20 licenses were also acquired for our users. The evaluation itself was performed on a UPenn system temporarily dedicated for DoD use (ultimately, a Walter Reed Eclipse workstation has to be transferred to the UPenn as part of this comprehensive solution).

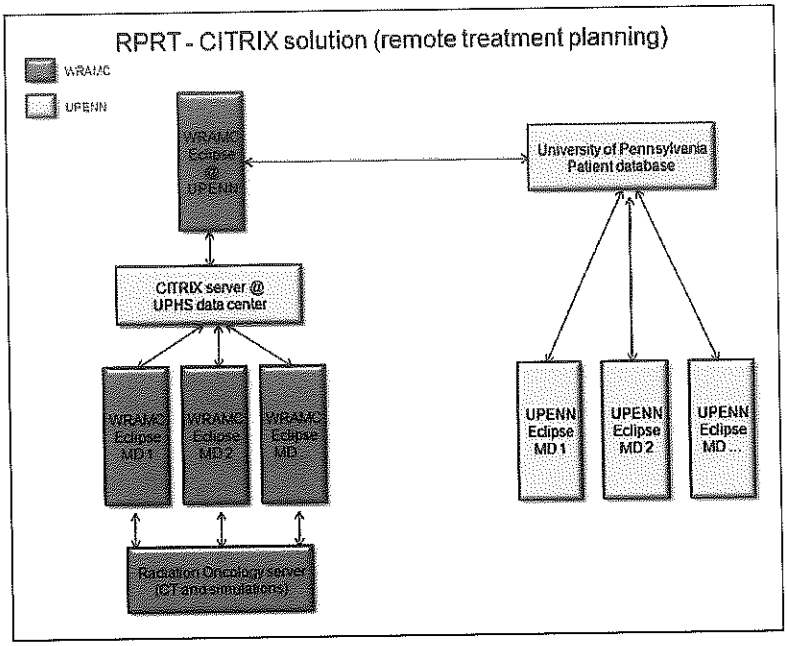

Fig. 2. Schematics of the hybrid solution (part 2).

Results

As the solution was being designed, our program developed a standard operating procedure (SOP) to account for the inclusion of telemedicine equipment for both communication and treatment planning purposes. Tests were conducted over a period of a year and a half to ascertain the robustness of the solution. Although the SOP offers two alternative ways of conducting proton treatment planning, our evaluation focused on "remote planning on Penn server from DoD MTF" (*Fig. 3*), which we feel provides the greatest benefit to the telemedicine community.

The testing of the VTC link itself took about 12 months, as connectivity problems persisted despite numerous software refreshes and reconfigurations. Although both Tandberg and Polycom equipments are intended to follow industry standards, compatibility issues prevented us from achieving full bilateral connectivity (failure by UPenn to receive video) until the Tandberg development team was able to replicate and test our setup in their own laboratory. Once the issue had been identified and corrected, a patch was applied to the Codian gateway, the Tandberg device that integrates ISDN and IP networks. Since then, our two sites have been able to enjoy full bilateral connectivity (audio and video).

The feedback from users has been overwhelmingly positive. Time delay, a limit of both hardware and bandwidth,[13,14] is a problem often reported by users of telemedicine systems. Our solution offers not only real-time feedback,[15,16] but also fluidity of motion and optimal resolution[17] for treatment planning.

Patient selection and enrollment occurs either on-site (weekly rotation of DoD radiation oncologists to UPenn) or remotely (telemedicine solution). Once enrolled into a proton radiotherapy course of treatment, the DoD patient is scanned at Walter Reed and the CT sets acquired are subsequently transferred from the servers to the local drive of the user's treatment planning workstation.

The CITRIX application itself is launched through a small "executable" (CITRIX Secure Access Client). Once the connection is established, users can then access the UPenn Intranet (UPHSNET) and, subsequently, the treatment planning application. The CITRIX encryption technology (AES 256-bit) guarantees the integrity of any protected health information being transmitted over the Internet, as required by HIPAA. The UPenn Health System created a specific "user group" with rights to access the treatment planning package. Each user within that group (radiation oncologists, medical physicists, and dosimetrists) was assigned a specific login and password combination for both CITRIX and Eclipse access, further strengthening security.

Once the user has taken control of the workstation located at the UPenn (used to contour normal structures/targets and design treatment plans), the mapped "C:" drive allows the user to seamlessly import these files into the Eclipse software; the treatment plan subsequently generated is automatically saved on the UPenn patient server (i.e., no manual transfer of files required).

Any issues arising during the planning process, or the treatment itself, give rise to an ad-hoc call using the Tandberg 1700 MXP audio-videoconferencing units to examine and troubleshoot the issue dynamically.

This hybrid solution not only ensures the involvement of a DoD radiation oncologist in the proton planning of his or her patients, but also prevents a certain degree of redundancy, such as rescanning of patients (a time saving of up to several weeks) or restaging (identical immobilization devices at both sites).

Although our tests relied on three units (two of which had the multisite functionality), this SOP assumes that all caregivers involved in remote proton planning will be equipped with both a high-definition desktop VTC unit (Tandberg 1700 MXP or Polycom 4000 HDX) and a CITRIX client on their treatment planning workstation.

Discussion

As network and computing capabilities improve, telemedicine is increasingly moving away from the now relatively trivial transfer of static images[18–20] to more complex clinical activities, such as telesurgery[21] or, in our case, dynamic treatment planning.

As reported in our previous publication, our initial prototype did not move past the testing phase, but we hope that satellite institutions will still view the Polycom PVX software solution as a cost-effective and worthwhile solution to conduct point-to-point (and multipoint, should a bridge be available as a resource) VGA-quality audio-videoconferences. In addition, its data collaboration features, whether those take the form of sharing a desktop (still images) or an application (dynamic collaboration), can greatly enhance the

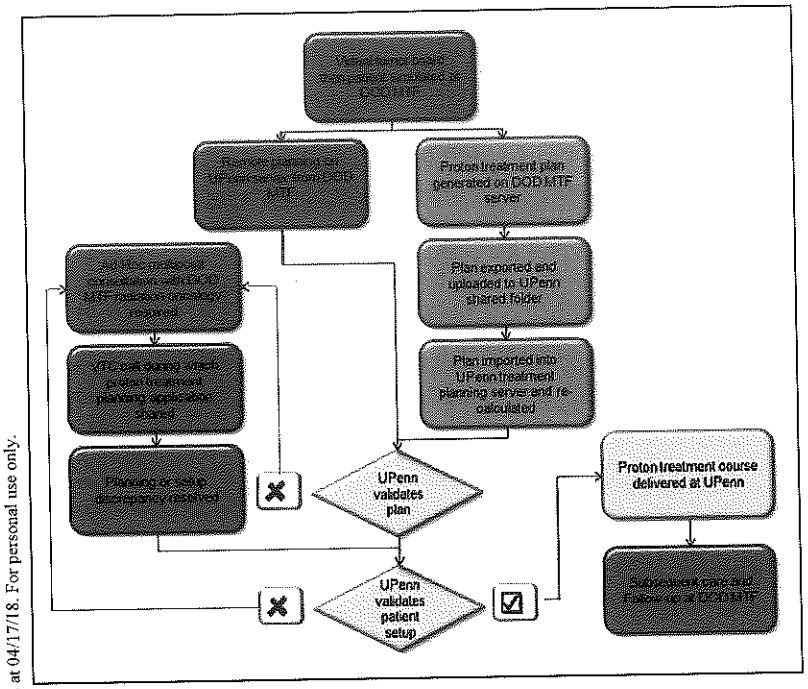

Fig. 3. Standard operation procedure (SOP) flowchart for the use of this solution in radiation therapy.

experience of far-site physicians seeking increased "involvement" in the treatment of their patients. In particular, we did welcome the capabilities of PVX to integrate with existing MCUs to accommodate desktop-driven conferences for more than two participants. For the field of radiation oncology, this product could provide main hospitals and their satellite institutions with a cost-effective platform to conduct both virtual tumor boards and dosimetry conferences with participating institutions.[22–25] Although this prototype solution was not adopted by our program, the lessons learned enabled us to develop the vastly superior system we have now (*Fig. 4*).

The choice to go with a hybrid system, one relying on ISDN and IP rather than IP alone, was guided by the fact that a DoD-run network exists to run audio-videoconferencing (MEDNET VLAN). We were further assured by the Walter Reed Directorate of Information Management that conducting VTCs over an ISDN line was a much more robust and secure approach.[26] Respecting patient privacy, and data security as a whole, we went by the guidelines offered to us and therefore went for an ISDN videoconferencing solution.

Our hybrid remote proton therapy treatment planning solution not only improves access to a scarce treatment modality[27,28] for both patient and provider, as a telemedicine solution, but also has the potential to bring the cumulative expertise of all oncology specialties (gynecological, medical, pediatric, surgical, and radiation) to extend collaboration and education among the cancer-care community.[29–32]

Although the cost of the hardware may present a budgetary challenge for smaller clinics,[33] the approach we propose will naturally scale upward as network capacities are expanding, giving users the ability to see and hear in high definition, while engaging in the real-time remote manipulation of complex treatment plans. The solution also gives users the ability to seamlessly interact, as if working side by side. The benefit to our patient community is also very real and quantifiable, as their time relocating to Philadelphia for treatment will be minimized because of the existence of this telemedicine solution (needlessness of repeating scans, simulations, and planning of treatment); in routine cases, the net time savings associated with this solution is estimated to be between 1 and 3 weeks per patient.

Conclusions

Our robust remote treatment planning telemedicine solution offers a path toward greater integration of military treatment facilities, or satellite clinics, into regional proton therapy centers.

PVX over I2 solution (assessement)

STRENGTHS

- software-based codec able to run on existing computers
- low-cost ($110 per license)
- ability to application-share (T120 protocol)
- impressive performance:
  - ability to transmit/receive VGA images at 15 FPS
  - ability to remotely plan treatment with real-time feedback

WEAKNESSES

- reliance on MANVT grant (no guarantee of continued funding)
- not integrated into existing clinical infrastructure
- would eventually escape the realm of 'academia and research' (I2 mandate)

Hybrid RPRT solution (assessment)

STRENGTHS

- integrated into existing clinical IT infrastructure
- potential to grow with expanding network capabilities (HD)
- user friendly
- requires little space
- multi-faceted use

WEAKNESSES

- cost ($8,000 per VTC unit)
- server-based application-sharing functionality (CITRIX) out of our control

Fig. 4. Strengths and weaknesses of both solutions.

Acknowledgments

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Disclaimer

The opinions, interpretations, conclusions, and recommendations in this article are those of the authors and are not necessarily endorsed by the US Army.

Disclosure Statement

No competing financial interests exist.

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Fiducial markers in prostate for kV imaging: quantification of visibility and optimization of imaging conditions

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Abstract

The purpose of this work is to investigate possible smaller, less-dense fiducial markers implantable into the prostate for target localization and patient repositioning verification in an on-board kV–kV imaging system on a proton gantry. The experiments used a pelvic phantom and a variety of commercially available fiducial markers: CIVCO carbon marker of ϕ; 1 $\times$ 3 mm, gold seed markers of ϕ; 0.8 $\times$ 3 mm and ϕ; 1.2 $\times$ 3 mm, and IBA Visicoil helical gold linear markers in diameters of 0.35, 0.50, 0.75 and 1.15 mm. Two orthogonal on-board kV imagers were arranged for digital radiographic imaging of the phantom through the lateral and anterior–posterior directions. The contrast-to-noise ratio (CNR) for a given marker was calculated and used as a quantitative measure of its visibility. The patient entrance skin exposure (ESE) was measured and parameterized for kVp, mAs and source-to-surface distance. The ratio of CNR to ESE was first introduced to characterize the efficiency for imaging a marker using a given x-ray technique in order to optimize the marker's visibility and simultaneously minimize the x-ray imaging dose. If CNR > 2, which corresponds to a significance $p < 0.05$, is required for acceptable visibility, the carbon marker and the smallest Visicoil marker are not suitable for imaging through dense bone but the others are capable of being employed in the clinic. It is predicted that other markers in development should have a greater thickness than equivalent of 0.14 mm thick gold in order to produce the acceptable visibility in the lateral kV imaging. The linear Visicoil marker of ϕ; 0.50 $\times$ 5 mm is most suitable for kV imaging in the prostate for proton therapy as it induces the least proton dose perturbation amongst the acceptable markers. An optimal range of 120–130 kVp and 40–80 mAs is

determined using the maximal CNR/ESE and CNR > 2 for laterally imaging this marker in the prostate.

(Some figures may appear in colour only in the online journal)

1. Introduction

Accurate localization and motion tracking of the patient's targeted tumor is crucial for precise delivery of radiation treatment. To reduce the uncertainty of target positioning during the course of treatment, inter- or intra-fractional imaging has been used to localize the target, leading to image-guided radiation therapy (IGRT). Studies have shown that IGRT can significantly minimize patient setup uncertainties and achieve better conformal radiation therapy (Schaly *et al* 2005, Chung *et al* 2009). In IGRT, imaging of bony anatomy is able to provide precise alignment for patient repositioning. However, more accurate prostate target localization commonly involves the use of implanted radiopaque fiducial markers due to the irregular motion of the prostate gland relative to bony anatomy (Chung *et al* 2004, Chen *et al* 2007, Kupelian *et al* 2008). In addition, continuous imaging of the implanted fiducial markers makes it possible for real-time tracking of prostate organ motion during treatment. Conventional solid gold seeds have been used for 3D real-time target tracking by combining simultaneous kV and MV imaging in external beam x-ray radiation therapy (Mao *et al* 2008, Luo *et al* 2008). In practice, three or more solid gold seed markers have been inserted in the prostate for better accuracy and reproducibility of daily prostate target alignment in order to reduce the localization uncertainty due to the migration of the seeds in the organ (Kudchadker *et al* 2009). Permanently implanted solid metallic markers within the target organ, however, can cause artifacts. Examples of the artifacts include distortion in CT imaging (the so-called metal artifact) and change of target density. The distorted CT image that is used for treatment planning can ultimately result in inaccurate delivery of the radiation dose if not accounted for (Wei *et al* 2006). A significant change in localized density results in a change of proton depth–dose characteristic, therefore interfering with proton beam therapy (Kwak *et al* 2007).

Many attempts have been made to develop the next-generation soft tissue fiducial markers. A suitable fiducial marker used in proton therapy should have (1) good visibility in kV imaging, (2) minimal distortion in CT imaging, (3) minimal dose perturbation for planned proton beam, (4) good biocompatibility with soft tissue and (5) great stability with negligible migration. Features 4 and 5 are not discussed in this study. The development of the next-generation fiducial markers has been carried out in three directions. One area is the construction of coil-like linear markers (Gates *et al* 2007). The IBA trade-marked Visicoil linear markers are constructed of various sized gold wires to form helical coils. The helical coil design of Visicoil provides extreme flexibility of the marker and allows the marker to conform with mobile soft tissue. Its hollow structure reduces the relative thickness of the radiopaque material and decreases the equivalent density of the marker, thus reducing the image artifact. The use of the Visicoil linear markers can also reduce the number of markers used in the prostate to only two as the two ends of a linear marker can determine two points in volume. The Visicoil markers have been used in IGRT for various anatomical sites (Teh *et al* 2007). The second area uses a mixture of low-density biocompatible materials and gold particles. Lim *et al* (2009) studied mixtures of microscopic gold particles and human-compatible polymers as potential fiducial markers for proton therapy for prostate cancer. They concluded that the proposed fiducials can achieve good radiographic visibility, low distortion of the depth–dose distribution and

few CT artifacts. The third area looks for suitable alternatives to the material of gold using lower-Z radiopaque materials. Newhauser *et al* (2007) compared stainless steel and titanium markers to the same sized gold markers and concluded that the visible stainless steel marker minimally perturbed the proton beam. De Langen *et al* (2007) studied a variety of commercial and homemade fiducial markers, recommending the use of new carbon and polymer fiducial markers in kV imaging. Their homemade polymer markers used an organic polymer named polyether ether ketone combined with radiopaque materials (e.g. stainless steel) in a range of concentration, allowing one to tune the radiopacity of the marker to the best compromise in visibility versus image distortion.

In this study, we investigated the commercially available Visicoil linear markers and the carbon marker and compared them to the conventional gold seed markers in a kV–kV imaging system installed on a proton gantry. The aim of this study was to choose the most suitable implantable fiducial marker for prostate cancer in proton therapy in terms of the tradeoff between its visibility and the fiducial-induced artifacts. In general, the smaller and less-dense the marker is, the less distortion it would create in CT images and proton depth–dose distributions. Therefore, justification of the best marker centers on assessment and comparison of the visibility versus the size and density of the markers used in a clinic imaging system. Recently, the M D Anderson group studied proton dose perturbations caused by those markers of Visicoil helical gold markers (Giebeler *et al* 2009) and the carbon marker (Cheung *et al* 2010). In both Monte Carlo simulation (Giebeler *et al* 2009) and radiochromic film measurements (Cheung *et al* 2010), it was demonstrated that the percent dose perturbation created by a larger marker would be bigger. In this paper, we quantify the visibility of the markers by contrast-to-noise ratios (CNRs) from analysis of digital radiographic images taken in a variety of x-ray techniques. The ratio of CNR to patient entrance skin exposure (ESE) is, for the first time, used to characterize the efficiency for imaging the markers. This metric accounts for the visibility while simultaneously minimizing the x-ray imaging dose. The results can be used to justify the best x-ray technique for each marker and to predict the radiographic visibility for other potential fiducial markers.

2. Methods and materials

2.1. On-board kV–kV imaging system

A pair of kV imagers has been installed on the standard IBA proton gantry at the Roberts Proton Therapy Center of the University of Pennsylvania Medical Center. Each of two identical on-board kV imagers consists of a flat-panel detector and an x-ray tube. These two imagers are orthogonally positioned for digital radiographic imaging through the lateral (Lat) and anterior–posterior (AP) directions for the verification of patient positioning before proton treatment. When a patient is positioned on the table for proton beam therapy, two flat-panel detectors on the proton gantry can slide out with one facing a x-ray tube in the proton treatment nozzle horizontally and another facing a tube under the floor on the gantry vertically as shown in figure 1. The source-to-imager distance and source-to-axis distance are 210.6 and 151 cm for the horizontal system (A), and 347 and 287.5 cm for the vertical system (B), providing magnification factors of 1.39 and 1.21 for the Lat and AP imaging, respectively. The x-ray tube (A-277, Varian Medical Systems, Palo Alto, CA) can operate from 40 to 150 kVp with a rotating 7° rhenium–tungsten molybdenum target and is available with the nominal focal spots of 0.6–1.0 mm. The actual focal spot used was 1.0 mm. The indirect flat-panel detector (PaxScan 4030E, Varian Medical Systems, Palo Alto, CA) is an amorphous silicon receptor featuring a sensitive area of 291 mm × 405 mm with a 0.2 mm thick

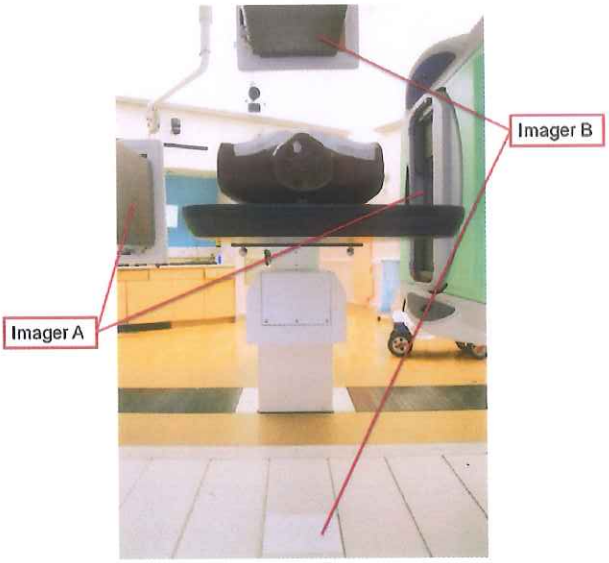

Figure 1. The experimental setup. A whole body phantom is positioned on a movable patient table with one kV system imaging through the lateral direction (horizontal imager A) and another through the anterior–posterior direction (vertical imager B).

DRZ-Plus (GSO(Tb)) scintillator plane. The size of pixel pitch is 0.127 mm featuring a limiting spatial resolution of 3.94 lp mm^{-1}. A pixel matrix of 2303 $\times$ 3200 is obtained for one radiographic image in full resolution mode. The horizontal (A) and vertical (B) imagers can operate separately or consecutively (B follows A after 5 s) with one generator supplying specified high voltage to both x-ray tubes. Consecutive, unlike simultaneous, imaging does not suffer from the interference between two imagers. The interference may contribute to the extra scatter component due to x-rays from the other tube which can in turn increase noise and decrease contrast resolution. A drawback for being unable to image simultaneously in these two orthogonal imagers is that it can be more complicated to precisely derive a 3D target position from two series of images due to patient motion between these two acquisitions.

2.2. *Phantom*

A whole-body humanoid Alderson non-sectioned RANDO phantom (Radiology Support Devices, Long Beach, CA) used in this study is shown on the patient table in figure 2(a). The phantom consists of highly detailed bony anatomy and soft tissue equivalent materials. Only the pelvic portion of the phantom was imaged by each of two kV imagers. This portion does not allow markers to be inserted into it. To simulate the effect of implanted fiducial markers in the prostate gland, the markers to be studied were attached on the right and left lateral sides of the phantom for imaging upstream and downstream along the x-ray beam. It is then assumed that the average of the results from both sides will be a good approximation of the result in the prostate in the lateral imaging taking into account the effect of the x-ray beam hardening and attenuation from the entrance to the prostate. The markers were imaged through dense femur bone or soft tissue to evaluate their visibilities through materials with different

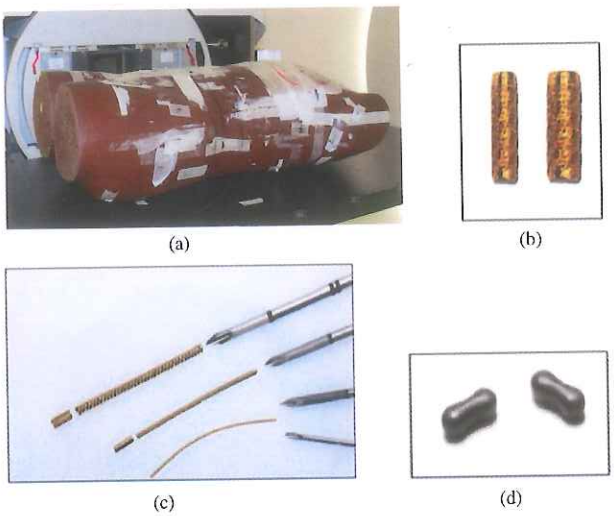

Figure 2. (a) The whole body humanoid phantom. (b) Two solid gold seed markers of 0.8 and 1.2 mm in diameter. (c) Three Visicoil linear markers of 1.15, 0.75 and 0.35 mm in diameter and 20 mm in length; the 1.2 and 0.8 mm solid gold markers are shown as comparisons. (d) The carbon markers with a dumbbell shape.

Table 1. Properties and characteristics of various fiducial markers used in the study.

Marker name	Diameter (mm)	Length (mm)	Thickness of radiopaque material (mm)	Density (g cm^{-3})
Gold 1.2	1.2	3	1.2	19.3
Gold 0.8	0.8	3	0.8	19.3
Visicoil 1.1	1.15	5, 10	1.0	15.3
Visicoil 0.75	0.75	5, 10	0.5	13.8
Visicoil 0.5	0.50	5, 10	0.3	13.1
Visicoil 0.35	0.35	5, 10	0.1	8.04
Carbon 1.0	~1.0*	3	~0.4	2.4[a]

[a] Assuming that the carbon marker is a cylindrical shape instead of a smaller dumbbell shape.

densities. For the AP imaging, the markers were simply placed on the anterior surface of the phantom through the pubic symphysis or pubic bone.

2.3. Fiducial markers

A variety of commercially available fiducial markers, CIVCO carbon marker of ϕ; 1.0 × 3 mm, gold seed markers of ϕ; 0.80 × 3 mm and ϕ; 1.2 × 3 mm (CIVCO Medical Solutions, Orange City, IA), and IBA Visicoil linear helical gold markers of ϕ; 0.35 mm with a wire of 0.05 mm in diameter, ϕ; 0.50 mm with a wire of 0.15 mm, ϕ; 0.75 mm with a wire of 0.25 mm, and ϕ; 1.15 mm with a wire of 0.50 mm (RadioMed Corp., Tyngsboro, MA), were investigated in this study. The properties and characteristics of the above fiducial markers are summarized in table 1. The thickness of the radiopaque material was determined to be the maximum length for an x-ray beam traversing through a cross-sectional plane. The two solid gold markers (Gold 1.2 and Gold 0.8) as shown in figure 2(b) are commonly used as

the standards in current radiotherapy for target localization. This study evaluates the next-generation fiducial markers, namely the Visicoil linear markers and the carbon marker. The Visicoil markers with four different diameters (Visicoil 1.1, 0.75, 0.5 and 0.35) and two different lengths of 5 and 10 mm were used to evaluate the tradeoff between the fiducial-induced artifacts and the radiographic visibility in the prostate gland. The Visicoil 1.1, 0.75 and 0.35 with a length of 20 mm are shown in figure 2(c). Both the artifacts and visibility are dependent on the attenuation coefficient and thickness of the radiopaque material used in the marker. The density of each Visicoil marker was calculated by assuming that the marker is immersed in soft tissues and is listed in table 1. The carbon marker shown in figure 2(d) was constructed to form a dumbbell shape to prevent migration in soft tissues. It consists of a carbon fiber shell containing the radiopaque material of zirconium dioxide (ZrO_2) with a density of 5.68 g cm^{-3}, representing a less-dense low-Z solid marker for an alternative to the standard solid gold markers. The average density of 2.4 g cm^{-3} listed in table 1 for the carbon marker was calculated by assuming a cylindrical shape for the marker and its filler ZrO_2 with an estimated diameter of 0.4 mm for the filler.

2.4. Image processing

The acquired digital radiographic images in raw formats were processed using AMIDE (A Medical Imaging Data Examiner), a free tool for viewing, analyzing and registering volumetric medical imaging data sets (http://amide.sourceforge.net/). Several regular shapes including box, intensity-thresholded isocontours and/or manually selected areas can be chosen to form regions of interest (ROIs). For selected ROIs, AMIDE computes and yields the mean and standard deviation of pixel values in each ROI. For each imaged marker, two ROIs were chosen for the marker signal and its surrounding background (soft tissue or bone region). The CNR for the marker was then calculated using the means and standard deviations from the ROIs as

$$\mathrm{CNR} = \frac{|N_m - N_b|}{\sqrt{\sigma_m^2 + \sigma_b^2}}, \tag{1}$$

where N_m and σ_m are the mean and standard deviation of pixel values for the marker ROI while N_b and σ_b are the mean and standard deviation for the corresponding soft tissue or bone ROI. The CNR defined in equation (1) is similar to the signal-to-noise ratio (SNR). In general, the SNR describes an imaging object in contrast to its surrounding background (normally in air) where the background signal is assigned to zero. It is understood that the bigger the CNR or SNR, the better the contrast resolution to reliably identify an object. Therefore, the CNR can be used as a quantitative measure of the visibility of the marker. According to Rose's criterion (Rose 1973), the SNR needs to be greater than 5 for a 100% probability to identify a target from an environment of white noise with a mean of zero. Luo *et al* (2008) showed that it would be invisible if the observed CNR falls under 1 in kV imaging. In fact, the CNR defined in equation (1) is identical to the t-value in a student test for two sets of measurements (Hendee and Ritenour 2002). As the number of degrees of freedom (NDF) increases, the t distribution approaches the Gaussian distribution. For a significance level of 0.05 to distinguish two measurements, it requires $t > 1.96$ for very large NDF or $t > 2.23$ for NDF $= 10$. In digital radiographic imaging, each pixel value in a flat-panel detector can be regarded as an independent measurement. The number of pixels in a ROI limits NDF. In our measurements, the number of pixels in the smallest ROI for the smallest marker is larger than 100. Therefore, in this paper, we required the measured CNR > 2 as a universal criterion

Table 2. Measured CNRs for various fiducial markers in the lateral imaging through soft tissue (soft) or dense femur bone (bone) at different x-ray technique factors.

X-ray technique		Gold 1.2		Gold 0.8		Visicoil 1.1		Visicoil 0.75		Visicoil 0.5		Visicoil 0.35		Carbon 1.0	
kVp	mAs	Soft	Bone	Soft	Bone	Soft	Bone	Soft	Bone	Soft	Bone	Soft	Bone	Soft	Bone
75	25	0.44	0.12	0.48	0.09	0.45	0.18	0.40	0.18	0.37	0.19	0.21	0.07	0.34	0.21
	50	1.05	0.38	0.84	0.26	0.75	0.26	0.75	0.24	0.74	0.27	0.49	0.17	0.48	0.15
	100	1.84	0.62	1.63	0.43	1.51	0.53	1.26	0.50	1.29	0.40	0.93	0.28	0.86	0.45
	200	2.99	0.88	2.71	0.75	2.46	0.94	2.30	1.02	1.99	0.68	1.44	0.46	1.45	0.51
	500	4.03	1.26	3.93	1.49	3.76	1.43	3.07	1.35	2.78	0.95	1.72	0.50	2.07	0.79
100	5	0.54	0.19	0.51	0.20	0.44	0.19	0.47	0.19	0.39	0.17	0.22	0.08	0.31	0.09
	10	1.00	0.39	0.96	0.34	0.84	0.35	0.75	0.44	0.68	0.30	0.43	0.11	0.52	0.14
	25	2.31	0.80	1.92	0.80	1.97	0.84	1.65	0.88	1.49	0.70	0.95	0.26	0.97	0.24
	50	3.93	1.54	3.30	1.43	3.35	1.53	2.79	1.61	2.68	1.21	1.76	0.46	1.75	0.55
	100	5.91	2.44	4.21	2.15	4.86	2.30	4.12	2.19	4.16	1.93	3.11	0.91	2.50	0.80
	200	7.26	4.05	5.43	3.45	6.09	3.45	5.16	2.92	5.01	2.39	4.07	1.30	3.28	1.41
125	5	1.36	0.48	1.21	0.46	1.11	0.61	1.05	0.56	0.82	0.44	0.50	0.16	0.46	0.14
	10	2.22	0.89	1.95	0.78	2.01	0.98	1.63	0.94	1.51	0.72	0.96	0.36	0.86	0.22
	25	4.41	1.85	3.62	1.73	3.71	2.01	3.32	1.99	3.09	1.53	2.04	0.61	1.68	0.53
	50	6.10	2.95	4.39	2.69	5.45	3.07	4.69	2.74	4.44	2.20	3.34	1.12	2.49	0.86
	100	7.12	4.07	5.31	3.61	6.63	4.02	5.55	3.28	5.57	2.79	4.61	1.64	3.25	1.37
	200	7.93	4.93	5.49	4.48	7.40	4.97	6.14	3.78	6.29	3.16	5.43	2.12	3.92	1.94
150	5	2.01	0.89	1.81	0.83	1.76	0.89	1.64	0.93	1.41	0.72	0.80	0.25	0.72	0.19
	10	3.45	1.55	2.85	1.28	2.92	1.47	2.64	1.50	2.49	1.17	1.49	0.50	1.09	0.42
	25	5.55	2.74	4.38	2.60	4.88	2.83	4.43	2.59	4.10	2.16	2.84	0.91	1.94	0.58
	50	6.83	4.08	5.14	3.57	6.49	3.86	5.49	3.30	5.25	2.70	4.47	1.59	2.74	1.11
	100	7.39	5.01	5.41	3.99	7.07	4.66	6.10	3.88	5.98	3.05	5.48	1.94	3.39	1.52

for clearly visible markers in the prostate, which approximately corresponds to the commonly accepted probability of significance $p < 0.05$.

2.5. Optimizing x-ray technique

It is well understood that better image quality (visibility, spatial resolution, contrast resolution, etc) would be achieved by increasing x-ray kVp and/or mAs because more photons could be emitted and detected. However, the x-ray exposure would also be increased as a result of increased energy fluence by both kVp and mAs, resulting in an increased absorbed dose for patients. To achieve the best compromise for the image quality and radiation dose, we measured the CNRs of the markers and x-ray exposures in a wide range of x-ray technique factors for kV imaging. The voltages selected in the Lat imaging were 75, 100, 125 and 150 kV. Their corresponding values of mAs are listed in table 2. For AP imaging, only 75, 100 and 125 kVp were selected because of reduced thickness in the AP direction for the phantom/patients.

To compare the doses absorbed by the same patient under different x-ray techniques, knowledge of patient ESE should be sufficient. An exposure meter (Piranha, RTI Electronics, Fairfield, NJ) was used to measure the exposures at different x-ray settings of kVp and mAs. To optimize the x-ray technique, the ratio of CNR to ESE is calculated for characterizing the efficiency for imaging a marker. The ratio can be used to optimize the marker's visibility and simultaneously minimize the x-ray imaging dose.

The clearest radiographic image for each marker was acquired at 125 kVp and 200 mAs in a variety of selected x-ray techniques. The marker signal ROI was auto-contoured by a carefully selected intensity threshold for most markers except for the smallest Visicoil marker

and the carbon marker, where the manual contouring was needed for a clear boundary from the surrounding background of dense femur bone. The background ROIs were boxes with 20 × 40, 20 × 60 and 20 × 120 pixels corresponding to the signals of 3, 5 and 10 mm long markers, respectively. The same ROIs determined at 125 kVp and 200 mAs were applied to other images acquired at other x-ray settings for the same experimental setup of the same marker(s).

3. Results

3.1. Measurements of x-ray exposure

The RTI Piranha meter was positioned at a distance of 133 cm to the source for imager A or 301 cm for imager B for exposure measurements at a variety of kVp and mAs. The x-ray exposure linearity with mAs has been tested at 70 kVp for imagers A and B, yielding nonlinearity coefficients (defined as the sum of squared fractional residuals) of 0.04 and 0.06, respectively. Measured x-ray exposure per mAs has been fitted to kVp in a range of 50–125 kVp by a power law (Johns and Cunningham 1983) for imagers A and B, yielding exponents of 2.03 and 2.17, respectively. Ultimately, the x-ray exposure X at any given kVp, mAs and at a point of d cm to the source can then be estimated as

$$X(\text{mR}) = 6.51 \bullet \text{mAs}\frac{(\text{kVp})^{2.03}}{[d(\text{cm})]^2} \tag{2}$$

for imager A and

$$X(\text{mR}) = 2.32 \bullet \text{mAs}\frac{(\text{kVp})^{2.17}}{[d(\text{cm})]^2} \tag{3}$$

for imager B. The difference between the scaling coefficients can be attributed to different filtrations in two imagers and different exponents for kVp.

From equation (2), for example, when a patient is positioned on the table being imaged by imager A at 125 kVp and 50 mAs with a source-to-surface distance (SSD) of 133 cm, the ESE would be 333 mR, resulting in a maximum dose of approximately 0.31 cGy in the photon depth–dose distribution if an average roentgen-to-rad conversion factor of 0.93 for muscle is used. In comparison, the ESE at another x-ray technique of 100 kVp and 200 mAs would be 845 mR or the maximum dose of 0.79 cGy, resulting in a rise of ~150%. For the AP imaging with an SSD of 274 cm, the ESE at 90 kVp and 125 mAs is 67 mR or a dose of 0.063 cGy. If the technique of 125 kVp and 25 mAs is used, the ESE would be 27 mR or a dose of 0.026 cGy, resulting in a reduction of ~60%. A change from 100 kVp and 200 mAs to 125 kVp and 50 mAs for the lateral imaging alone would reduce the total imaging dose by about 19 cGy during the whole course of treatment assuming 40 fractions and x-ray kV imaging at least once for each fraction.

3.2. Uncertainty of CNR measurements

The uncertainty of CNR measurements was estimated by analyzing the results of experiments repeated for the same marker at the same x-ray technique. The experiments repeated include those by (1) repeating in short time intervals of seconds in the same setup, (2) removing and replacing the marker in the same setup, and (3) setting completely different setups after days/months. Major deviations of the CNR measurements occurred for completely different setups from months apart. All of those results are consistent within ± 10%. For instance, two CNR measurements of the 5 mm long Visicoil 0.5 marker for the AP imaging through the

pubic symphysis at 100 kVp and 100 mAs are 5.5 and 6.5 from 2 months apart, yielding a fractional standard deviation of 8.3%. Combining the results from those repeating experiments, we estimated the uncertainty of the CNR measurements to be 10% for either inter- or intra-fractional monitoring.

3.3. Comparison of CNRs of Visicoil fiducials in different lengths

The comparison of four different sized Visicoil markers with the lengths of 5 or 10 mm has been made in the lateral imaging. Both 5 and 10 mm long markers were positioned at the lateral sides by femur bone or by soft tissue. Shown in figures 3(e)–(f) are enlarged images where the prostate gland could be contained for a male for the markers of Visicoil 1.1, 0.75, 0.5 and 0.35 in the lateral kV imaging at 125 kVp and 200 mAs. The measured CNR for the biggest Visicoil 1.1 marker in 10 mm length increases ~15% compared to that in 5 mm length. The increase of 15% is insignificant compared to the 10% uncertainty and may be attributed to non-identical conditions of the measurements. The CNRs for the other Visicoil markers change little by reducing the length from 10 to 5 mm. Henceforth, we will report results only for those 5 mm long Visicoil markers.

3.4. Measured CNRs for various markers in lateral imaging

The markers were positioned on both the right and left hip sides of the pelvic phantom for upstream and downstream lateral imaging. These two measured CNRs have been averaged to estimate the CNR in the prostate for the lateral imaging. It is observed that for all markers, the downstream CNRs through femur bone are bigger (e.g. ~50% and ~25% larger for Gold 1.2 and Visicoil 0.5, respectively) than those upstream. The downstream CNRs through soft tissue are comparable to those upstream. Figure 3 shows enlarged images for various markers on the right hip side imaging upstream through femur bone and soft tissue at 125 kVp and 200 mAs. It is difficult to visualize the smallest Visicoil 0.35 marker and the carbon marker in the region of dense femur bone. Those markers should be within the ellipses shown in figures 3(f) and (h), corresponding to CNRs of 1.5 and 1.3, respectively. This illustrates and justifies our criterion of CNR > 2. The averaged CNRs for various markers are listed in table 2.

The measured CNRs from table 2 for all seven types of markers at 125 kVp are plotted as a function of mAs in figure 4. The results in the lateral imaging through soft tissue are shown in figure 4(a) and those through dense bone in figure 4(b). The curves connecting the data points from the same marker are to guide eyes only. The dotted line at CNR $= 2$ shows the accepted level for the radiographic visibility of the markers. It is evident from figure 4(b) that the CNRs for the carbon marker and the smallest Visicoil 0.35 marker in the region of dense femur bone are below the accepted level for almost the whole range of mAs.

The measured CNRs for all seven different types of markers at 125 kVp and 100 mAs in the lateral imaging through dense femur bone are plotted in figure 5 as a function of their gold equivalent thicknesses. The error bars show the experimental uncertainty of 10%. Given the known thicknesses for all six gold material markers as listed in table 1, we use an empirical formula to fit the data of those markers, yielding

$$\mathrm{CNR} = 3.94 + 0.993 \ln(t_m), \tag{4}$$

where t_m is the gold equivalent thickness of a marker in the unit of mm. The solid line in figure 5 represents the fitted function.

The gold equivalent thickness of 0.062 mm for the carbon marker is estimated by finding a thickness for gold that produces the same transmission probability as that by 0.4 mm

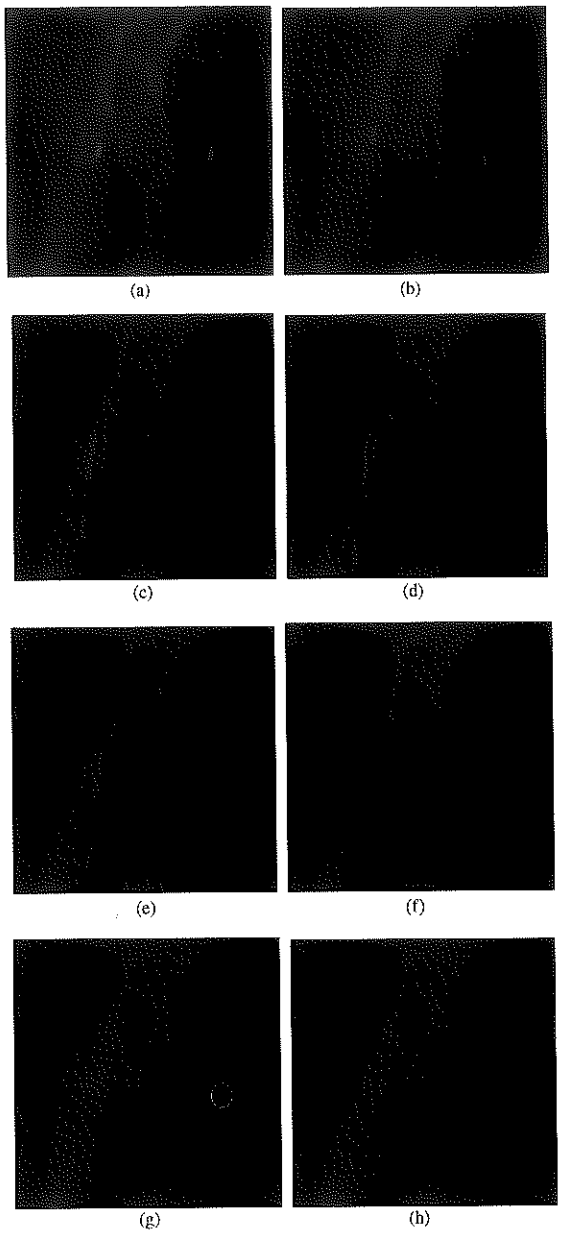

Figure 3. Enlarged images for the lateral kV imaging at 125 kVp and 200 mAs for the pelvic phantom. Different fiducial markers were positioned at the right hip side upstream through dense femur bone or soft tissue. (a) Gold 1.2 × 3 mm. (b) Gold 0.8 × 3 mm. (c) Visicoil 1.1 × 5, × 10 mm. (d) Visicoil 0.75 × 5, × 10 mm. (e) Visicoil 0.5 × 5, × 10 mm. (f) Visicoil 0.35 × 5, × 10 mm. (g) Carbon 1 × 3 mm (soft). (h) Carbon 1 × 3 mm (bone).

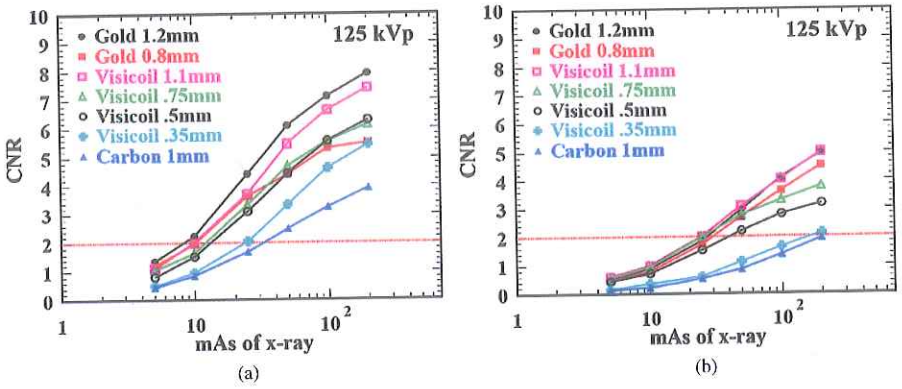

Figure 4. Measured CNR versus mAs of x-ray at 125 kVp for all seven types of markers in the lateral imaging through soft tissue (a) or through dense bone (b). The curves are to guide eyes for data points from the same marker.

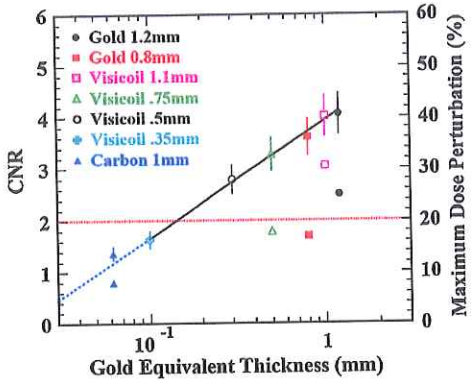

Figure 5. Measured CNR versus gold equivalent thickness for all seven different markers at 125 kVp and 100 mAs in the lateral imaging through dense femur bone. The solid line is a logarithmic fit to data of six gold markers of Gold 1.2 and 0.8 and Visicoil 1.1, 0.75, 0.5 and 0.35. The dashed line is an extrapolation of the fitted function. The percent maximum dose perturbations for Gold 1.2 and 0.8, Visicoil 1.1 and 0.75, and Carbon 1.0 are also plotted without error bars according to the right vertical axis. See details in the text.

ZrO_2 at 125 kVp. To compute the transmission probability for a given marker, the x-ray energy spectrum and energy distribution of attenuation coefficients of the marker need to be known. The x-ray energy spectrum for a tungsten target can be generated using the TASMIP algorithm (Boone and Seibert 1997). The energy distributions of attenuation coefficients for most elements and many compounds and mixtures can be found in the Physical Reference Database in the National Institute of Standards and Technology (Hubbell and Seltzer 2004). The attenuation coefficients for ZrO_2 can be calculated using mass weighted averages from those for both zirconium and oxygen. From an extrapolation of the fitted function to the CNR of the carbon marker, we in turn obtained a thickness of 0.50 mm for ZrO_2 material, which is bigger than the assumed value of 0.40 mm shown as the solid triangle in the far left side of

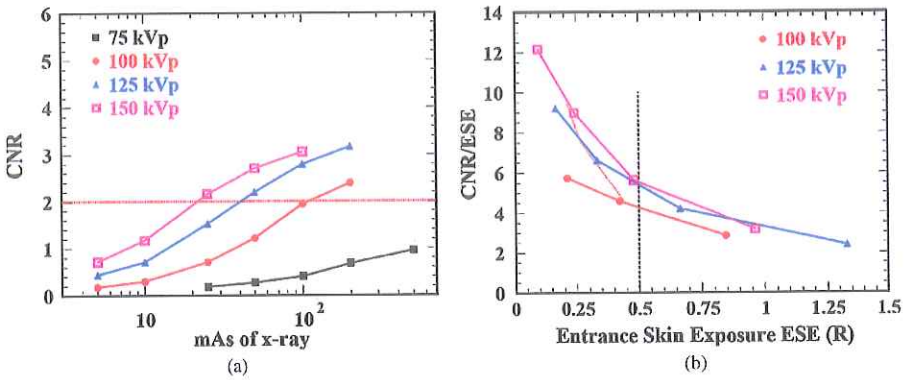

Figure 6. (a) Measured CNR versus mAs of x-ray at 75, 100, 125 and 150 kVp for the Visicoil linear marker of ϕ; 0.50 $\times$ 5 mm in the lateral imaging through dense bone. (b) Measured CNR per roentgen versus ESE for those data points with CNR $>$ 1 from (a). The dotted curve is for CNR $=$ 2 and the dashed line is for an exposure threshold of 500 mR. All solid curves in (a) and (b) are to guide eyes for data points at the same kVp.

figure 5. This thickness of 0.50 mm for the filler is still quite reasonable for the carbon marker that has a size of about 1 mm in the dumbbell shape. From the cross point of the fitted function and the dotted line at CNR $=$ 2, we predict that the thickness for an acceptable fiducial marker in the lateral kV imaging through dense femur bone should be greater than a gold equivalent of 0.14 mm.

To demonstrate the dose perturbation effect in proton therapy for the implanted markers of different size and material, we adopt the published data from the studies of the M D Anderson group for markers implanted perpendicular to incident proton beams. The dose shadows were observed downstream behind the markers. The percent maximum dose shadow was used to characterize the dose perturbation effect. The results of the percent maximum dose perturbations for Visicoil 1.1 and Visicoil 0.75 in a water equivalent depth of 22 cm were -30.5% and -17.9%, respectively, by Monte Carlo simulations (Giebeler *et al* 2009). No results were available for smaller Visicoil 0.5 and Visicoil 0.35. The results for Gold 1.2, Gold 0.8 and Carbon 1.0 in a water equivalent depth of 23.5 cm were -25%, -17% and -8%, respectively, by radiochromic film measurements (Cheung *et al* 2010). The uncertainty of the maximum dose perturbation is on the order of 5% for both the Monte Carlo simulation results and measurements. The absolute values of the percent maximum dose perturbations for those markers are plotted without error bars in figure 5 for comparison. It is demonstrated that the percent dose perturbation created by a marker with smaller gold equivalent thickness would be less under the comparable condition.

Figure 5 also shows that the smallest acceptable marker is Visicoil 0.5 with 0.3 mm gold in thickness, which represents the best compromise between the visibility and proton dose perturbation. We then plotted the CNRs for the Visicoil 0.5 marker at different kVp and mAs in figure 6(a) for the lateral imaging through dense bone. The curves are to guide eyes for data points with the same kVp. It is observed that mAs $>$ 100 at 100 kVp, mAs $>$ 40 at 125 kVp or mAs $>$ 20 at 150 kVp is required for the Visicoil 0.5 marker to be clearly visible in the lateral kV imaging through femur bone. We calculated the ESEs at SSD $=$ 133 cm for those data points with the CNR $>$ 1 as shown in figure 6(a) and plotted the ratio of CNR to ESE as a function of the ESE in figure 6(b). The dotted curve is for CNR $=$ 2 and the dashed line is for

Table 3. Measured CNRs for various fiducial markers in the AP imaging through the pubic symphysis at different x-ray technique factors.

X-ray technique		Gold	Gold	Visicoil	Visicoil	Visicoil	Visicoil	Carbon
kVp	mAs	1.2	0.8	1.1	0.75	0.5	0.35	1.0
75	25	1.16	1.22	1.17	0.97	0.68	0.40	0.70
	50	2.12	2.21	2.4	1.88	1.68	1.30	1.43
	100	3.68	3.82	3.95	3.09	2.35	1.76	2.48
	200	5.04	5.59	5.58	4.74	3.76	2.99	3.84
	500	5.46	6.23	7.01	6.51	4.53	4.53	4.58
100	5	0.87	0.84	0.85	0.76	0.57	0.35	0.48
	10	1.68	1.76	1.74	1.50	1.16	0.44	0.86
	25	3.63	3.83	3.91	3.28	2.68	1.81	1.82
	50	4.82	5.2	5.62	4.74	3.59	2.8	2.95
	100	5.41	5.9	6.78	6.75	5.51	4.32	4.11
	200	5.72	6.74	6.98	7.56	7.28	5.04	4.98
125	5	1.72	1.76	1.90	1.39	1.08	0.84	0.8
	10	2.99	3.11	3.27	2.36	2.34	1.42	1.47
	25	4.65	5.19	5.54	5.09	4.64	2.72	1.82
	50	5.38	6.18	7.23	6.71	6.11	4.18	4.18
	100	5.75	6.81	7.14	7.73	7.54	4.75	4.77
	200	5.88	6.49	7.56	8.22	7.74	5.5	5.11

an exposure threshold of 500 mR. It shows that the lower the exposure, the bigger the CNR per roentgen, thus the more efficient for imaging the marker. It also shows that the CNR/ESE increases as kVp increases and saturates at ~125 kVp. Figure 6(b) demonstrates that a region enclosed by the dotted and dashed curves would simultaneously fulfill the requirements of CNR $>$ 2 and ESE $<$ 500 mR. It has been established that the tissue contrast in radiographic x-ray imaging increases as the x-ray energy (or kVp) decreases (Hendee and Ritenour 2002). Therefore, when the CNR/ESE is comparable (within uncertainty) for 125 kVp and 150 kVp, imaging at 125 kVp is superior to 150 kVp for its better tissue contrast. Ultimately, an optimal range of 120–130 kVp and 40–80 mAs is determined using the maximal CNR/ESE and CNR $>$ 2 for laterally imaging the Visicoil 0.5 marker in the prostate.

3.5. Measured CNRs in AP imaging

For the AP imaging of the pelvic phantom, we simply positioned the markers on the anterior surface of the phantom. Figure 7 shows enlarged images for various markers on the AP imaging through the pubic symphysis or pubic bone at 100 kVp and 100 mAs. All markers can easily be visualized. The measured CNRs for all seven types of markers at 100 kVp are plotted as a function of mAs in figure 8(a) for the AP imaging through the pubic symphysis and in figure 8(b) for those through pubic bone. The CNRs slightly decrease for imaging through pubic bone relative to imaging through the pubic symphysis. When the tube current–time product exceeds 40 mAs at 100 kVp, the CNRs are greater than 2 for all markers. The measured CNRs for various markers in the AP imaging through the pubic symphysis are listed in table 3.

The CNRs for the Visicoil 0.5 marker at different kVp and mAs are shown in figure 9(a) for imaging through pubic bone. Figure 9(a) shows that mAs $>$ 100 at 75 kVp, mAs $>$ 20 at 100 kVp or mAs $>$ 10 at 125 kVp is required for the Visicoil 0.5 marker in the AP imaging. The ESEs at SSD = 274 cm for those data points with the CNR $>$ 1 as shown in figure 9(a) are calculated. The CNR/ESE versus ESE is plotted in figure 9(b). The dotted curve is for

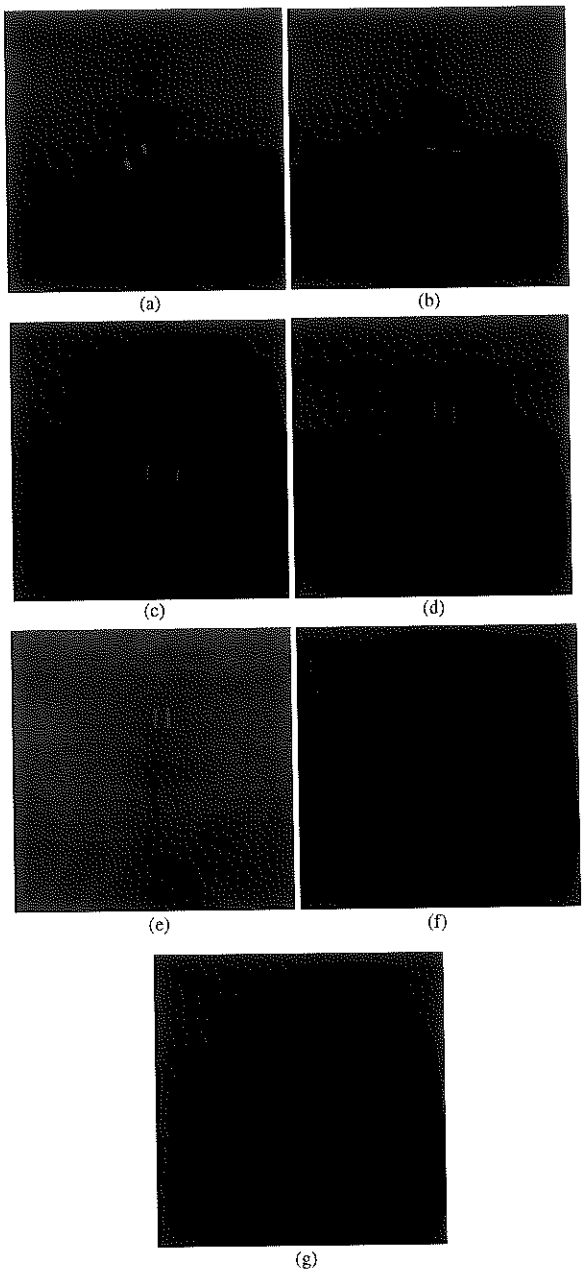

Figure 7. Enlarged images for the AP imaging at 100 kVp and 100 mAs for the pelvic phantom. Different fiducial markers were positioned at the anterior surface of the phantom through pubic bone or through the pubic symphysis. (a) Gold 1.2 × 3 mm. (b) Gold 0.8 × 3 mm. (c) Visicoil 1.1 × 5 mm. (d) Visicoil 0.75 × 5 mm. (e) Visicoil 0.50 × 5 mm. (f) Visicoil 0.35 × 5 mm. (g) Carbon 1.0 × 3 mm.

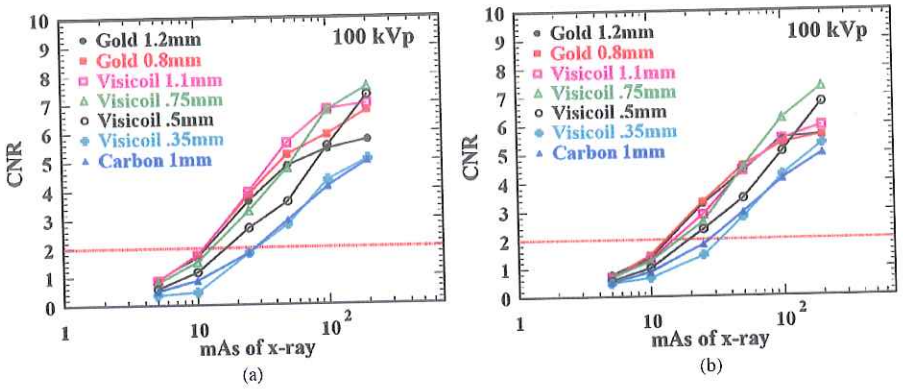

Figure 8. Measured CNR versus mAs of x-ray at 100 kVp for all seven types of markers in the AP imaging through the pubic symphysis (a) or through pubic bone (b). The curves are to guide eyes for data points from the same marker.

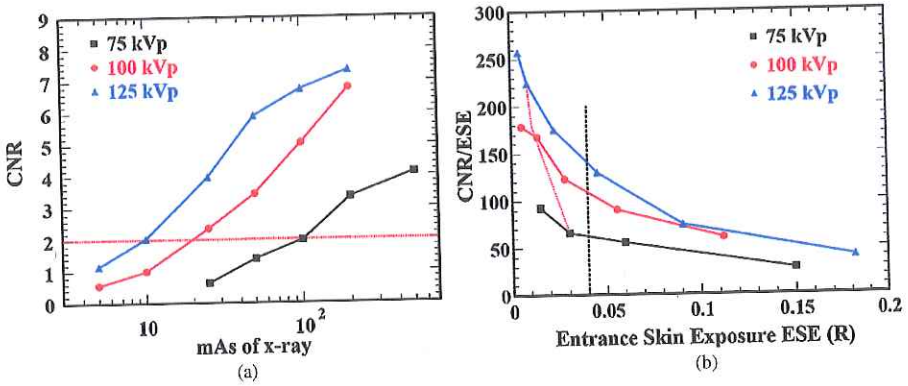

Figure 9. (a) Measured CNR versus mAs of x-ray at 75, 100 and 125 kVp for the Visicoil linear marker of ϕ; 0.50 $\times$ 5 mm in the AP imaging through pubic bone. (b) Measured CNR/ESE versus ESE for those data points with CNR $>$ 1 from (a). The dotted curve is for CNR $=$ 2 and the dashed line is for an exposure threshold of 40 mR. All solid curves in (a) and (b) are to guide eyes for data points at the same kVp.

CNR $=$ 2 and the dashed line is for an exposure threshold of 40 mR. An optimal range of 120–130 kVp and 10–40 mAs is determined by maximizing the CNR/ESE and requiring CNR $>$ 2 for imaging through the AP direction.

The carbon marker is difficult to visualize in the lateral imaging through dense bone as shown in figure 3(h). Nevertheless the carbon marker can produce acceptable visibility in the Lat imaging through soft tissue (figure 10(a)) and in the AP imaging (figure 10(b)).

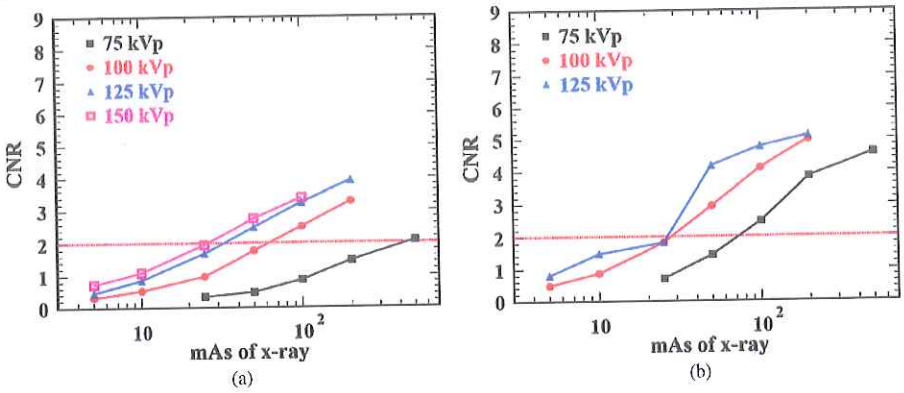

Figure 10. Measured CNR versus mAs of x-ray for the carbon marker at 75, 100, 125 and 150 kVp in the Lat imaging through soft tissues (a) and at 75, 100 and 125 kVp in the AP imaging through pubic symphysis (b). The curves are to guide eyes for data points at the same kVp.

4. Discussion

The most suitable fiducial marker in proton beam therapy for prostate cancer should achieve acceptable visibility with the lowest possible density. The helical gold marker of Visicoil 0.5 is the best compromise amongst the investigated fiducial markers.

It is evident that lateral imaging at 125 kVp and 100 mAs is superior to that at 100 kVp and 200 mAs taking into consideration both the visibility of the marker and x-ray radiation dose. The former generates bigger CNR and lower dose than the latter. Furthermore, this novel analysis of maximizing the ratio of CNR to ESE and requiring CNR > 2 has demonstrated improved imaging efficiency in an optimal range of the x-ray technique. It is therefore suggested that x-ray technique factors ranging in 120–130 kVp and 40–80 mAs can be used for the lateral imaging of this marker in the prostate, leading to a reduction of $\sim$20 cGy or $\sim$60% for the imaging dose compared to that using 100 kVp and 200 mAs during the whole course of treatment. The optimal range suggested here is, of course, for a patient with a size comparable to that of the RANDO phantom used in the study. For a bigger or smaller patient, a slight adjustment of a higher or lower range may be needed. The ratio CNR/ESE was chosen as the metric to maximize due to its simplicity. Other ratios that more heavily weight the visibility or dose may be suitable for other applications.

While a variety of means for real-time target imaging and tracking exists for conventional radiation therapy, it is not clear what would be an appropriate means to realize image guided proton therapy due in part to the complexity of the proton beam and limited space of the gantry room. A successful target localization and real-time motion monitoring system using electromagnetic tracking—the Calypso 4D localization system (Willoughby *et al* 2006, Langen *et al* 2008) suffered radiation damage in the proton treatment room reported from a test done in the Roberts Proton Therapy Center. Lately, the Calypso system was modified and demonstrated improved performance in February of 2011. Recently, Cho *et al* (2008) proposed a robust monoscopic method for real-time tumor tracking using combined occasional x-ray imaging and continuous external respiratory monitoring. The on-board AP x-ray kV imaging system on the proton gantry may provide the x-ray imaging in this method for real-time target and motion tracking in proton therapy.

Although the carbon marker is difficult to visualize in the lateral imaging through dense bone, it can produce acceptable visibility in the Lat imaging through soft tissue and in the AP imaging. Therefore, the carbon marker, the least dense marker, may still be suitable for use in other organs. The carbon marker may also be used in the prostate for the AP imaging to provide real-time target tracking as mentioned above and may induce the least dose perturbation of the proton beam.

5. Conclusion

No significant improvement is observed by increasing the length of the Visicoil linear markers from 5 to 10 mm. If CNR > 2 (~95% probability to identify markers from surrounding background) is required for acceptable visibility, the carbon marker and the smallest Visicoil 0.35 marker are not suitable for imaging through dense bone. The investigated Visicoil linear helical gold marker of ϕ; 0.50 $\times$ 5 mm is most suitable for the kV imaging through both soft tissue and dense bone for prostate cancer. This marker is visible in dense bone region and induces less perturbation to proton depth–dose distribution than other larger Visicoil linear markers and solid gold markers. In terms of optimizing the visibility and simultaneously minimizing the imaging dose, a range of 120–130 kVp and 40–80 mAs is determined using the maximal CNR/ESE and CNR > 2 for laterally imaging this marker in the prostate for standard sized male patients. It is predicted that other markers in development should have transmission probability of their radiopaque materials in equivalence to 0.14 mm thick gold in order to produce acceptable visibility in the kV x-ray radiographic imaging.

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