Quantification of Tumor and Organ at Risk (OAR) Volume and Motion Path Changes during Definitive Photon or Proton Beam Radiotherapy

Protocol #: IRB# 810302 / UPCC# 08909

Principal Investigators:

Charles B. Simone, II. MD
Assistant Professor
Department of Radiation Oncology
Perelman Center for Advanced Medicine
3400 Civic Center Boulevard
Philadelphia, PA 19104
(215)662-3998
charles.simone@uphs.upenn.edu

James McDonough PhD
Associate Professor
Division of Medical Physics
Department of Radiation Oncology
Perelman Center for Advanced Medicine
3400 Spruce Street
Philadelphia, PA 19104
(215) 615-5632
mcdonough@xrt.upenn.edu

Sub-Investigators:

Michelle Alonso-Basanta, MD, PhD
Smith Apisarnthanarax, MD
Keith Cengel, MD, PhD
John Christodouleas, MD, MPH
Jay Dorsey, MD, PhD
Zelig Tochner, MD
Neha Vapiwala, MD
Alex Lin, MD
Nathan Anderson, MA
Michael Bieda, MA
Stefan Both, PhD
Jarod Finlay, PhD
Edgar Ben-Josef, MD
Lilie Lin, MD
Robert Lustig, MD
James Metz, MD
John Plastaras, MD PhD
Eli Glatstein, MD
Stephen Hahn, MD
Ali Kasseea, PhD
Richard Maughan, PhD
Kevin Teo, PhD
Timothy Zhu, PhD

Statistician: Rosemarie Mick

Date: 11/13/2009
Amended: 05/10/2010 12/18/2013
Amended: 06/08/2010
Amended: 08/13/2010
Amended: 10/04/2010
Amended: 2/21/2011
06/06/2011
06/24/2011
1/20/2012
08/13/2012
03/28/2013

Table of Contents

List of Abbreviations

4D: 4 Dimensional
3D: 3 Dimensional
CT scan: Computed tomography scan
MR Scan: Magnetic Resonance Imaging Scan
NSCLC: Non Small Cell Lung Cancer
SCLC: Small Cell Lung Cancer
SUV value: Standardized Uptake Values
Gy: Gray
CTV: clinical tumor volume
PTV: planning target volume
GTV: gross tumor volume
ITV: internal tumor volume
PI: Principal Investigator
AE: Adverse Event
SAE: Serious Adverse Event
GI: Gastrointestinal
IRB: Institutional Review Board
ORP: Office of Research Protection
HRPO: Human Research Protection Office

Quantification of Tumor and Organ at Risk (OAR) Volume and Motion Path Changes during Definitive Photon or Proton Beam Radiotherapy

PROTOCOL OVERVIEW

In recent years, conformal techniques have been developed that allow for precise delivery of radiotherapy to the primary tumor and regional lymphatics while minimizing the dose to normal tissues. These approaches are predicated upon precise anatomic localization of the regions to be irradiated. Unfortunately, at present, most conformal treatment delivery approaches do not account for changes in tumor volume, tumor motion or changes in patient anatomy during the time course of definitive radiotherapy. Proton beam radiotherapy can potentially allow for ultra-precise delivery of treatment due to the physical characteristics of the proton beam. Therapeutic proton beam radiotherapy allows for the elimination of exit dose and a significant reduction in the entrance dose to the patient while maximizing dose delivered to the tumor (Figure 1). However, accurate treatment delivery with proton beam radiation is predicated upon precise definition of tumor volume and location. Tumor volume reduction during definitive proton beam radiotherapy has resulted in significant dosing errors, with dose deposition in unintended regions (MDACC PTCOG 47). The purpose of this protocol is to quantify the extent of tumor volume, motion, and anatomic changes that occur during the tumor course of definitive photon beam radiotherapy. As both proton beam and photon beam radiotherapy have nearly identical biological efficacy, the changes observed during photon beam radiotherapy should closely approximate that which would likely be observed during proton beam irradiation.

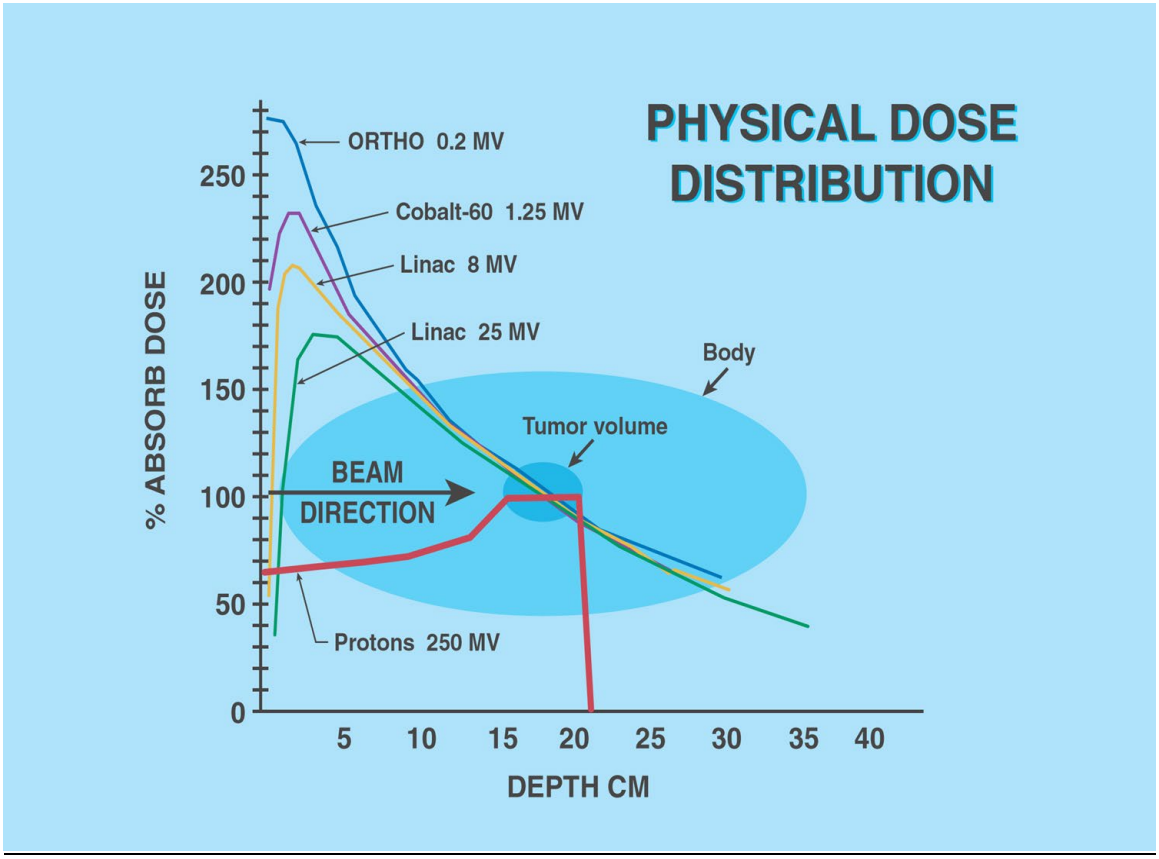


Figure 1: Comparison of Dose Deposition between Photon and Proton Beam Radiotherapy

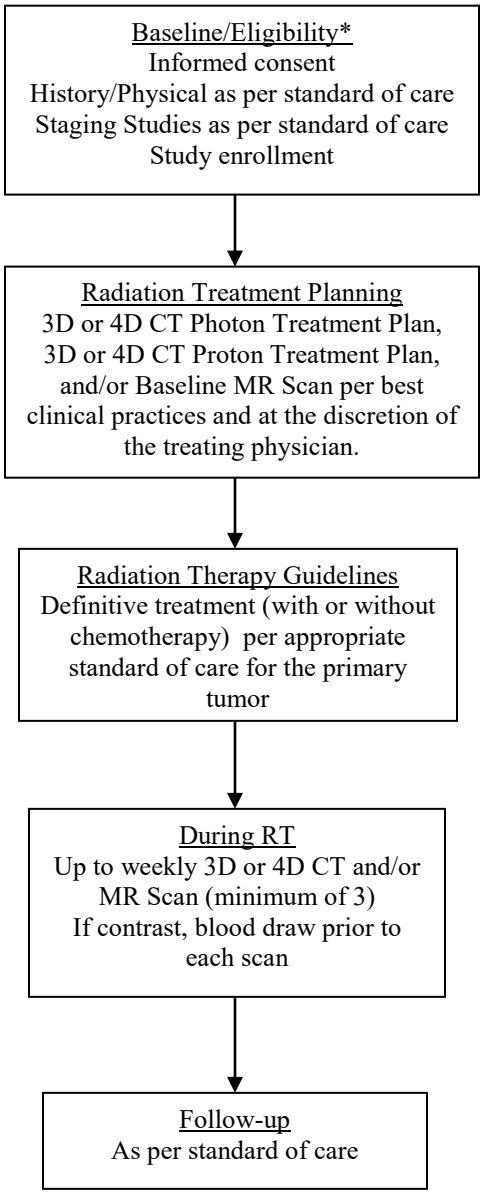
SPECIFIC AIMS/OBJECTIVES

Overall Aim
To estimate the degree of tumor volume, tumor motion, and patient anatomy changes that occur during the time course of definitive photon and proton beam radiotherapy. We further intend to quantify the dosimetric error that would occur in patients receiving proton beam radiotherapy if these changes are not accounted for.

Primary Aim
To estimate the degree of tumor volume, tumor motion and patient anatomy change during treatment with photon beam radiotherapy using 4D or 3D CT Scans and/or a serial of MR Imaging.

Secondary Aims
To utilize the data generated from the photon or proton beam patients to simulate and estimate the degree of error if tumor volume, tumor motion path and patient anatomy changes are unaccounted for during treatment with proton beam radiotherapy by generating simulated serial proton plans with this data.

METHODS/METHODOLOGY



*Baseline/eligibility procedures, including informed consent, may occur at any time from consultation until radiation therapy treatment begins.

All subjects' data will receive a standardized analysis. A descriptive analysis will be performed to determine tumor volume changes, tumor motion changes and patient anatomy changes. We will also evaluate the variations in the dose distribution to targeted volumes and normal tissues that occur with tumor and patient anatomy changes. These variations in dose distribution will be compared between photon treatment plans and proton treatment plans.

ELIGIBILITY

- Patients with biopsy proven NSCLC, SCLC, Head and Neck Cancer, Gastrointestinal cancer (including but not limited to colorectal and rectal cancers), or Gynecological malignancy requiring definitive radiotherapy with or without chemotherapy.

REQUIRED SAMPLE SIZE

- 30 patients per treatment site for a total of 120 patients.

STUDY DESIGN

- This is a pilot study to evaluate the changes in tumor volume, tumor motion, patient anatomy and dose distribution during the course of radiation treatment using up to weekly CT and/or MR Scans with the potential usage of contrast during the imaging procedure. We will analyze the effect of tumor changes and patient anatomy changes on radiation treatment efficacy.

1.0 ABSTRACT

In recent years, conformal techniques have been developed that allow for precise delivery of radiotherapy to the primary tumor and regional lymphatics while minimizing the dose to normal tissues. Unfortunately, at present, most conformal treatment delivery approaches do not account for changes in tumor volume, tumor motion or changes in patient anatomy during the time course of treatment. Studies have shown that lung, head and neck, and gynecological tumors can change significantly during radiation treatment. Patients can lose significant weight during the radiation treatment, which can alter the patient's body habitus and anatomy. These tumor and anatomical changes can alter radiation dose distribution, resulting in higher radiation doses to normal tissue and lower radiation doses to target volumes. Adapting for changes in tumor motion, tumor volume and patient anatomy can therefore enhance radiation treatment efficacy and widen the therapeutic ratio. Because proton beams require precise target definition, accounting for tumor changes should be critical when using proton beam radiation treatment.

This is a pilot study to quantify the tumor and organ at risk volume and motion path changes that occur during definitive proton beam or photon beam radiotherapy. The patients will undergo CT scans in treatment planning position at the time of CT Simulation. Photon beam treatment plans and proton beam treatment plans will be generated from these images. Based on the location of the primary tumor, patients will undergo either up to weekly 3D or 4D CT and/or a serial of MR scans during treatment. These images will be compared to the initial CT and/or MR scans used for treatment planning and analyzed for changes in tumor volume and tumor anatomic location. At the end of treatment, the /serial images will be compared to the initial treatment planning images to quantify the changes in tumor volume and tumor motion during the course of radiation treatment. Each CT and/or MR scan will also be used to evaluate the changes in dose distribution to the target volumes and normal tissues that occur with the initial photon treatment plan and initial proton treatment plan. The changes in tumor volume, tumor motion and dose distribution during the course of radiation treatment will be analyzed to determine the effect of tumor changes on radiation treatment efficacy.

2.0 BACKGROUND AND SIGNIFICANCE

Radiation therapy is a form of treatment used to control many cancers including lung cancers, head and neck malignancies, cancers of the gastrointestinal tract and gynecological cancers. One important challenge of radiation treatment is the balance between delivering adequate radiation dose to the tumor while controlling for radiation induced toxicity. Radiation induced toxicity is caused by incidental radiation delivery to critical normal structures in proximity to the tumor. The amount of incidental radiation dose is dependent upon the tumor volume, location and margins needed to account for planning and setup error. The volumes are determined during radiation treatment planning and are based on patient imaging done during a simulation appointment prior to radiation treatment. In cancers with a propensity for movement secondary to respiratory motion, such as lung, and some gastrointestinal cancers, 4D CT planning is often implemented. This form of image guided treatment planning takes into account

respiratory motion when calculating appropriate target volume margins. The distal esophagus can move 0.8cm radially and 1.8cm axially (Yaremko) and the pancreas can move 2.4 +/- 1.6 cm axially (Bussels). Lung tumors are significantly affected by respiratory motion and move 5-10 mm during quiet breathing and as much as 4.5 cm (Stevens) with deeper breaths. Therefore, accounting for respiratory motion can be extremely important for targeted radiation therapy.

The course of radiation treatment often lasts longer than 8 weeks. For patients with head and neck and gastrointestinal cancers, maintaining adequate nutrition during this time can be challenging. Studies have shown that about 35% of patients with head and neck cancers experience >10% weight loss and patients with gastrointestinal cancers experience weight loss ranging from 0-12% (Milano, Talamonti, Lin). Significant weight loss results in changes in patient anatomy, which can distort radiation dose distribution and therefore treatment efficacy.

In addition to patient anatomy the size of the tumor as well as the anatomic location of the tumor are subject to change during radiation treatment. Fox et al. demonstrated a median GTV reduction of 44.3% at 50Gy in patients with non-small cell lung cancer. Head and neck cancers and cervical cancers are particularly sensitive to radiation effects. Barker et al. demonstrated a 69.5% reduction in GTV volume with a median mass displacement of 3.3mm at the end of radiation treatment in patients with head and neck cancers. Cervical cancers have a median mid treatment regression rate of 69% at 36-45Gy when treated with radiation alone and 79% when treated with concurrent chemoradiation (Nam). The resulting anatomic changes during radiation treatment can have a significant impact on dosimetric distributions, resulting in inadequate dose delivery to the tumor even with 4D CT image guided radiotherapy planning (Britton). Britton et al. evaluated the dosimetric consequences of anatomic changes during conformal photon beam radiotherapy for 10 patients with NSCLC using weekly 4D CT Scans. The authors noted a substantial decrease (-20.5%) in the PTV dose coverage and variable increases in dose to normal tissue structures such as the lung, spinal cord, esophagus and heart. These variations were due to inter and intrafractional variations during treatment.

Ideally, one would account for both inter-and intrafraction variability on a daily basis or after a given number of fractions. (Vanuytsel, Vansteenkiste et al. 2000) This could widen the therapeutic ratio by maximizing dose to the tumor and protecting critical normal structures. Harsolia et al. found that in the treatment of patients with NSCLC, daily respiratory motion and tumor volume correction yielded the maximal decrease in treatment volumes (44% reduction) and the maximal decrease in volume normal lung irradiated (31% reduction) and mean lung dose (31% reduction).

At present, the standard of care is to base the entire course of radiation treatment upon the initial treatment plan, which is derived from the pre-treatment scan. It is easy to envision that treatment re-planning to adjust for anatomical changes may be necessary during the course of radiation treatment. The overall objective of this study is to determine the

extent of tumor volume, tumor motion and patient anatomy variation during radiation treatment.

While tumor anatomic changes are important in radiation treatment with photon therapy, these factors are of particular concern when implementing proton therapy. Unlike photon beams, proton beams can deliver radiation that enters the body at low doses, but then uniformly delivers high doses of radiation to the tumor followed by a steep fall-off exit dose. These features allow high doses of radiation to be delivered to the primary tumor, with lower toxicity to normal tissue. Because of the sharp demarcations between low dose and high dose areas, proton therapy requires accurate delineation of the primary tumor in order to deliver adequate radiation dose to the tumor while limiting normal tissue toxicity. Therefore, adjusting for anatomic changes in tumors during radiation treatment is particularly important in proton therapy. Hui et al. studied the effect of anatomic changes on proton therapy dose distribution in lung cancer using weekly 4D CT Scans. Although only 8 patients were examined, there was variation in the CTV density as radiation treatment progressed. The authors concluded, however, that CTV coverage is adequate if tumor motion is taken into consideration with 4D CT planning. Interestingly, this CTV density variation was correlated with normal tissue toxicity, implying that as the tumor shrinks from radiation treatment, the high dose radiation spills over to normal tissue. The secondary objective of our study will be to utilize the serial imaging obtained from either the photon beam or proton beam patients to generate serial proton beam plans. This will allow us to estimate the dosimetric error with proton beam radiotherapy if tumor and patient anatomical changes are not accounted for during treatment.

We propose to quantify the changes in tumor volume, motion, and anatomic changes that occur during the time course of definitive radiotherapy in patients with lung cancers, head and neck cancers, gastrointestinal cancers (including but not limited to colorectal and rectal cancers) and gynecological cancers. These cancers were chosen as they represent the oncologic subsets that experience the greatest dynamic range in these variables during treatment.

3.0 SPECIFIC AIMS/OBJECTIVES

Specific Aim 1: To estimate the degree of tumor volume, tumor motion and patient anatomy change during treatment with photon beam radiotherapy.

1a. To estimate the degree and impact of tumor volume change during the course of definitive photon radiotherapy treatment in lung cancers, head and neck cancers, gastrointestinal cancers (including but not limited to colorectal and rectal cancers) and gynecological cancers.

1b. To estimate the degree and impact of tumor motion (anatomic location) change during the course of definitive photon radiotherapy treatment in lung cancers, head and neck cancers, gastrointestinal cancers (including but not limited to colorectal and rectal cancers and gynecological cancers.

1c. To estimate the degree and impact of changes in patient anatomy during the course of definitive photon radiotherapy treatment in head and neck and upper gastrointestinal cancers.

Hypothesis: Tumor volume and motion will change over the course of radiation treatment in patients with lung cancers, head and neck cancers, gastrointestinal cancers (including but not limited to coloorectal and rectal cancers) and gynecological cancers. The weight loss experienced by patients with upper gastrointestinal and head and neck cancers will have a significant impact on their anatomy. These changes will alter the dose distribution of the photon beam treatment plans, possibly limiting radiation dose delivery to the target volumes and increasing radiation toxicity to surrounding critical structures.

Specific Aim 2: To estimate the error if tumor volume, tumor motion and patient anatomy change during treatment with proton beam radiotherapy.

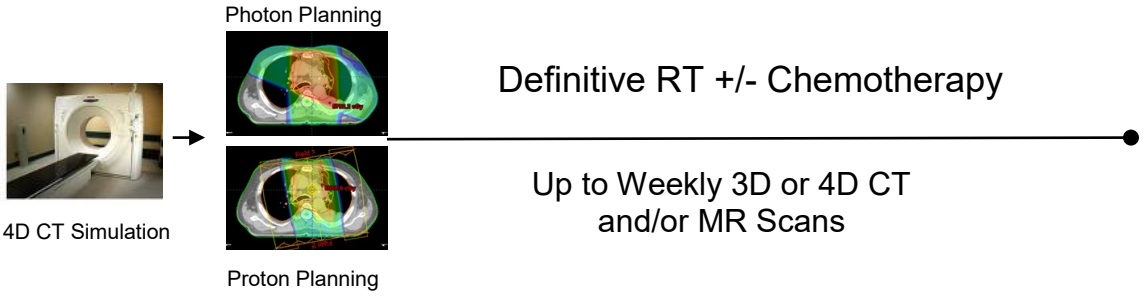
2a. To generate simulated proton beam plans using serial CT or MR imaging obtained from either photon or proton beam patients to estimate the dosimetric error if these changes are unaccounted for during proton treatment.

Hypothesis: The changes in tumor volume and motion and patient anatomy will have a greater effect on appropriate dose distribution in plans using proton beam therapy compared to photon beam therapy given the need for more accurate target delineation in proton beam therapy.

4.0 STUDY OVERVIEW

This is a pilot study to estimate the degree of tumor volume, tumor motion and patient anatomy change during treatment with photon or proton beam radiotherapy. Patients will undergo simulation with an MR scan and/or CT scan per best clinical practices, and 4D

imaging will be employed as indicated, at the discretion of the treating radiation oncologist. Photon beam treatment plans and Proton beam treatment plans will be generated from these images. Based on the location of the primary tumor, patients will undergo either up to weekly 3D or 4D CT and/or serial MR scans during treatment. These images will be compared to the initial CT/MR scans used for treatment planning and analyzed for changes in tumor volume and tumor anatomic location. At the end of treatment, the frequent 3D or 4D CT and/or serial MR images will be compared to the initial treatment planning images to quantify the changes in tumor volume and tumor motion during the course of radiation treatment. Each CT and/or MR Scan will also be used to evaluate the changes in dose distribution to the target volumes and normal tissues that occur with the initial photon treatment plan and initial proton treatment. The changes in tumor volume, tumor motion and dose distribution during the course of radiation treatment will be analyzed to determine the effect of tumor changes on radiation treatment efficacy.



5.0 PARTICIPANT SELECTION

5.1 *Inclusion Criteria*

1. Patients aged ≥ 18
2. Biopsy proven diagnosis of non-small cell lung cancer, small cell lung cancer, head and neck, esophageal, gastric, pancreatic, hepatic, billiary, colorectal, anal , cervical, endometrial, vaginal, vulvar, ovarian cancer and any other gastrointestinal or gynecological cancers requiring definitive radiotherapy alone with or without concurrent chemotherapy.
3. Able to provide written informed consent and comply with all study procedures
4. Entire course of radiotherapy will be delivered at the University of Pennsylvania Perelman Center for Advanced Medicine.

5.2 *Exclusion Criteria*

1. Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

5.3 *Recruitment Procedures*

Subjects will be recruited from the Oncology practices at Penn Medical Center. Patients will be referred by their physicians and include men and women who will be receiving radiotherapy with definitive intent with or without chemotherapy. Subjects will undergo an informed consent process in accordance with GCP. Informed consent will be obtained prior to the performance of any research specific (i.e. not standard of care) procedures and prior to the start of radiation therapy treatment. Subjects must meet all of the inclusion and none of the exclusion criteria as determined by baseline/eligibility 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 the Clinical Research Coordinator (CRC) in the Radiation Oncology department at the University of Pennsylvania and initiate introduction to the CRC. The treating radiation oncologist and/or CRC will interview the potential subject with privacy considerations, explain the requirements of the study and provide a copy of the Informed Consent Form. The treating radiation oncologist and/or CRC will state the volunteer nature of research and advise 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 research specific (i.e. not standard of care) procedures will be performed. Through use of the subject's electronic medical record and questions asked by the treating physician and/or CRC, patient eligibility based upon the inclusion/exclusion criteria will be verified. After the eligibility is established and confirmed with the treating physician/study investigator, a subject study number will be issued. All members of the research team will have successfully completed patient oriented research training. **Subjects will receive all treatment in the Radiation Oncology clinic of the University of Pennsylvania.**

6. 0 STUDY PROCEDURES

6.1 Institutional and Investigator Requirements

All patients must have a signed Informed Consent Form and a 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 cabinet to which only members of the study team will have access. 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.

HIPAA Compliance:

Patients will be asked to read and sign a combined study consent form and HIPAA consent 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.

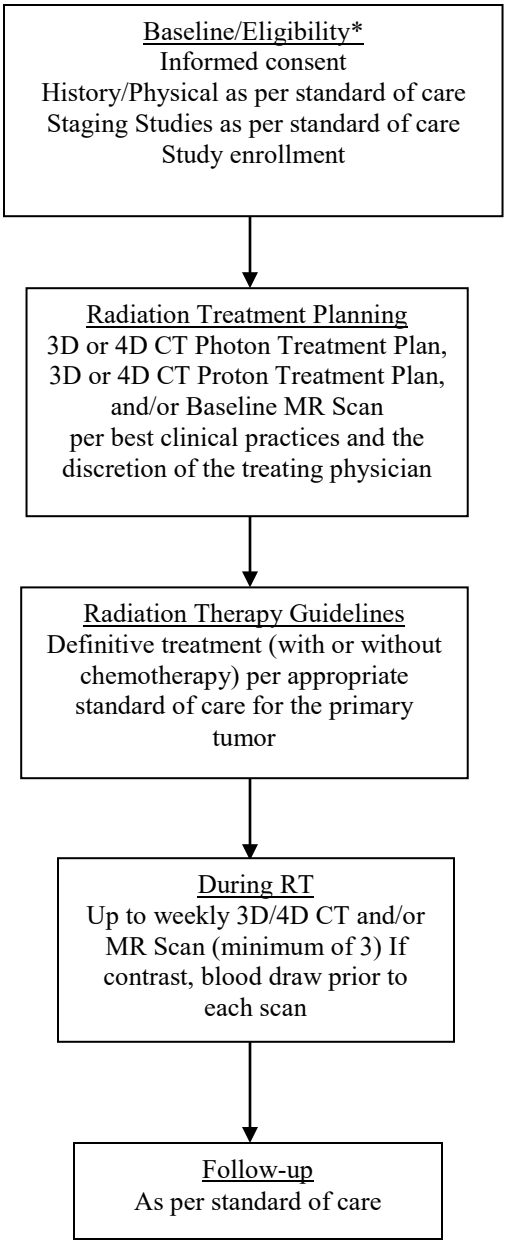
- Each subject will sign a combined study informed consent/ HIPAA authorization form prior to study entry.
- Each subject will be assigned a study number. All research-related material (to include specimens for research) will be labeled with the subject study number and the subject's initials.
- A list of the subject names with the associated subject numbers will be maintained by computer to which only members of the study team will have access.
- All research subject records will be kept in a study chart.
- An electronic database will be maintained. No subject names will be used in this database. Study numbers will be used. Only data which constitutes a limited data set (as defined by the University of Pennsylvania Health System in the HIPAA Privacy Education website) will be used.

6.1.1 *Potential Risks to Patient*

Patients have additional radiation exposure with weekly 3D/ 4D CT and/or serial MR scans. The additional patient dose from a single CT scan is typically less than 10 cGy. This dose is less than 0.2% of a typical definitive treatment of 5,000cGy to 7,000cGy, and compares to the additive dose from portal images that have been used as standard of care in radiation oncology departments throughout the United States for decades. The added risk from additional radiation exposure due to these weekly scans therefore is minimal. There is no additional radiation risk from an MR scan.

Depending on specific diagnosis, the treating physician may elect to order the imaging (MR, CT, or MR/CT) with contrast. This involves giving intravenous gadolinium (for an MRI) or intravenous iodinated contrast (for a CT) before that specific scan to better visualize your tumor and internal anatomy. Gadolinium and iodine can pose a risk to people with kidney disease. This risk is not anticipated but this remains a possible risk that will require monitoring through blood drawn to measure kidney functions prior to each imaging scan during radiation treatment.

6.2 *IRB Approval and Informed Consent*



*Baseline/eligibility procedures, including informed consent, may occur at any time from consultation until radiation therapy treatment begins.

6.3. Accrual Goals and Monitoring

Patients will be referred by their physician by calling the Clinical Research Coordinator (CRC) in the Radiation Oncology department at the University of Pennsylvania. Patient eligibility will be verified based upon based upon the criteria outlined in Section 4.1. and Section 4.2. After eligibility is established and confirmed, a subject study number will be issued. We anticipate enrollment of four-five patients per month onto this study.

6.4. Study Calendar / Schedule

Event	Baseline/Eligibility	Prior to RT Initiation	Weekly during RT
Informed Consent	X*	X*	
History and Physical	X	X	
Photon and Proton Treatment Planning and/or Baseline MR scan	X	X	
3D/4D CT and/or MR scans (determined by tumor location and treating physician)			X*
Blood Draw (prior to each imaging scan during RT)**		X	X

* *These are research specific procedures. All other procedures are standard of care.*

** *Only if receiving contrast with imaging).*

6.5. Pre-Registration /Pre-Treatment

Baseline/Eligibility

See Section 5.3 (Subject Recruitment and Screening) and Section 5.1 and 5.2 (Inclusion and Exclusion Criteria).

Radiation Treatment Planning

The radiation dose will be prescribed at mid-separation on the central ray for two equally weighted beams. For all other beam arrangements, the dose will be prescribed at the center of the target area or at the intersection of central rays of the beams.

Simulation for all fields is required for treatment planning. Patients will undergo simulation with an MR scan and/or CT scan per best clinical practices, and 4D imaging will be employed as indicated, at the discretion of the treating radiation oncologist. The 4D CT will be used to define the target volumes. The gross tumor volume (GTV) will consist of all known sites of disease including the primary tumor and all pathologically enlarged ($\geq$ 1 cm in short axis) positive lymph nodes prior to accounting for respiratory motion. Discontinuous volumes are allowed. In 4D planning CTs, the GTV will be

expanded to create an internal tumor volume (ITV), which will include the GTV and the extent of GTV respiratory movement as defined by the 4D CT. The clinical tumor volume (CTV) and planning target volume (PTV) will be constructed from the GTV by an automatic margining tool supervised and edited by the treating radiation oncologist. The irradiation target volume will be defined by shaped ports with custom-made blocks or multileaf collimation. Portal verification shall be done for all treated fields. Megavoltage equipment is required with minimum peak photon energies of 6 MV. SAD techniques should be used. Each field will be treated every session. Interruptions in therapy should be discussed with the principal investigator but will be instituted at the discretion of the attending radiation oncologist.

Dose calculation should be performed using inhomogeniety corrections to account for differences in tissue density across the thorax. The total dose to gross disease will be 40-80 Gy, depending on the standard of care for using radiotherapy to treat the primary tumor (with or without concurrent chemotherapy) and on the site of the primary tumor. The prescribed total dose and dose per day will be constrained to adjust for the standard normal tissue dose limitations.

RADIOTHERAPY PLANNING

Forward photon and proton beam plans will be generated on the CT simulation data set. These plans will be then be applied to the up to weekly data sets to quantify variance in dose deposition.

Treatment planning is not routinely changed during the course of radiation therapy. However, if it is found by the treating physician that a significant change has occurred in tumor volume, position or anatomy that render the original plan no longer optimal, then a new treatment plan will be created for the remainder of treatment. Should this occur, the PI will be notified of the treatment changes.

6.6. On Treatments

Based on the primary tumor location and the discretion of the treating radiation oncologist, atients will undergo 3D/4D CT Scan (up to weekly)) and/or MR Scan (minimum of 3).. The GTV, ITV and critical normal structures will be contoured on each up to weekly/serial scan. The up to weekly/serial GTV volume will be compared to the initial GTV volume to determine changes in tumor volume. Each GTV will be compared to the initial ITV volume to determine what percent of the GTV resides within the initial ITV. This value will be used to evaluate changes in tumor motion. Each ITV will be compared to the initial ITV. The initial photon treatment plan and proton treatment plan will be applied to the new scan. The amount of radiation dose to each GTV, ITV and critical normal structures will be recorded to determine the changes in dose distribution that occur as treatment progresses. **SUBJECTS WILL RECEIVE ALL SCANS IN THE RADIATION ONCOLOGY CLINIC OF THE UNIVERSITY OF PENNSYLVANIA**.

6.7. Post Therapy/Treatment:

Subjects will present for an initial post-treatment visit approximately 4-6 weeks after completion of radiation treatment as per the standard of care. Additional follow-up visits will be performed as per the standard of care. Subjects will be considered "off study" on the date of their last radiation treatment.

6.8. Criteria for Removal from Study

Any subjects experiencing a serious adverse event (SAE) felt to be related to the study imaging or imaging contrast will be withdrawn from the study. Subjects will be withdrawn from the study if discontinuation of treatment is deemed necessary by the principal investigator to be in their best interest (e.g. an abnormal response of the subject's malignancy to radiotherapy outside of normal limits is observed, intolerable side effects of radiotherapy occur, clinical deterioration occurs). Subjects may be withdrawn at any time at the discretion of the PI. Any subject withdrawing their consent to participate in the study or their authorization to use their protected health information will be withdrawn from the study. Subjects withdrawn may be replaced at the discretion of the principal investigator.

Subjects may also be withdrawn due to any of the following:

1. Failure to attend outpatient and treatment visits
2. Failure to cooperate and provide tolerability measures

Once the subject has discontinued the study, the primary reason for discontinuing the study must be clearly documented in the subject's records and on the CRF. The investigator will assess each subject for response at the time of withdrawal.

6.9 *Imaging Acquisition, Archival, and Interpretation*

All images will be acquired at the Hospital of the University of Pennsylvania or the Perelman Center for Advanced Medicine. Image acquisition, archival, and interpretation will be through the Departments of Radiation Oncology and Radiology at the University of Pennsylvania.

7.0 DATA COLLECTION AND MANAGEMENT

All subjects must have a signed Informed Consent Form and a confirmation of eligibility form filled out and signed by a participating investigator prior to receiving a study number.

Case report forms will be used to standardize data keeping and allow entry to a computerized data base.

Flow of Subject Data

Study entry: Each subject will be evaluated for this study based upon the inclusion and exclusion criteria. If a subject is interested in participating, he/she will be asked to sign and informed consent document after which an eligibility checklist will be completed and

signed. The subject will then be assigned a study number. All study forms: eligibility forms, on study forms, case report forms (CRF), and data entry forms will be coded with the subject's study number to protect subject confidentiality.

Imaging: Copies of all imaging for these studies will be maintained by the Department of Radiology at the University of Pennsylvania.

Follow-up: Follow up visits will occur as per the standard of care. Subjects will be considered off study as of the date of their last radiation treatment.

8.0 Safety and Adverse Events

The investigator and/or designated research staff will be responsible for detecting, documenting and reporting all events that meet the definition of an Adverse Event (AE) or Serious Adverse Event (SAE) felt to be related to the study imaging or imaging contrast. (see section 6.8)

9.0 STATISTICAL CONSIDERATIONS

9.1 *Background:*

Tumor volume, location and proximity to critical normal organs are determined by CT scans prior to the start of radiation treatment. Radiation dosimetry plans are not re-calibrated during the course of a patient's treatment since it is assumed that changes in these variables are negligible. This hypothesis has rarely been studied in a rigorous manner. Dramatic tumor shrinkage or patient weight loss, may cause the radiation energy beam to over-shoot the treatment target and may also increase the radiation dose to nearby critical normal organs.

9.2 *Study Design:*

This pilot study will determine changes over time in tumor volume and motion and patient anatomy, as well as dose distributions to normal organs. The study will inform medical decision-making about the need for (and timing of) re-calibration of radiation dosimetry plans. Up to weekly CT and/or serial MR scans (minimum of 3) will be employed to measure changes in tumor volume and motion and patient anatomy in patients receiving definitive radiation therapy (with or without concurrent chemotherapy). This study is <u>not</u> designed to evaluate the CT or MR procedure. CT or MR is simply the imaging method used for precise measurement of tumor volume variables. Enrollment will be stratified by disease site: NSCLC, Head & Neck, GI and Gynecologic tumors. The study will enroll 30 patients in each stratum. This study is descriptive and not powered hypothesis testing.

9.3 Objectives: To determine changes over time in:

1. tumor volume variables
2. tumor motion
3. patient anatomy
4. dose distribution to tumor and critical normal organs

9.4 Endpoints: To be measured at baseline and then weekly during 7-8 weeks of radiotherapy

1. GTV (gross tumor volume), the volume of the primary tumor visualized on the CT scan
2. ITV (interior tumor volume), the GTV expanded to include interior motion (i.e., breathing or swallowing) such that the tumor resides within the ITV during normal motion
3. CTV (clinical tumor volume), the ITV expanded to include microscopic disease (margins)
4. PTV (planning tumor volume), the CTV expanded by several mm, as determined by radiation dosimetry planning, PTV is considered the ultimate target volume

NOTE the relationship: GTV < ITV < CTV < PTV

5. Dose coverage: at each scan time point, determine the percent of the GTV which resides within the baseline ITV or CTV
5. patient weight and percent weight loss from baseline
6. Radiation dose to critical normal organs based on dose-volume histograms (i.e., 20 Gy to 50% of normal lung tissue)

9.5 Plans for Data Analysis: To be conducted within each stratum

1. Tumor Volume: To determine the distributions of volume variables and percent change from baseline. At each scan time point, compute mean, median, range and standard deviation of these variables and plot mean values over time. To compare volume variables at <u>baseline</u> to the values at selected scan time points by paired Wilcoxon signed ranks test.
2. Tumor Motion: At each scan time point, compute mean, median, range and standard deviation of the dose coverage and plot mean values over time. To compare ITV or CTV variables at <u>baseline</u> to the GTV at selected scan time points by paired Wilcoxon signed ranks test.
3. Patient Anatomy: To determine the distribution of patient percent weight loss. At each scan time point, compute mean, median, range and standard deviation of percent weight loss and plot mean values over time.
4. Dose distribution: To determine the distributions of radiation dose to GTV, ITV and critical normal organs. To correlate radiation dose to normal organs with percent weight loss.
5. Conduct exploratory longitudinal analyses to examine changes over time in the 30 patients. Random effects linear regression models will be employed to estimate changes in variables over time clustered by patient. Natural log transformation will be applied prior to modeling.
6. To assess if changes in volume variables are clinically relevant and if so, identify the earliest time point at which re-calibration is warranted. Although it may not be possible to identify a single ‘re-calibration solution’ for all patients in a particular stratum, we will attempt to identify the earliest scan time point at which the majority of patients have clinically important changes in tumor volume or location resulting in over-shoot of the target volume and/or increased dose exposure to normal organs.

9.6 Sample Size/Study Duration

Patient heterogeneity (e.g., size and location of the tumor, radiation dose/fractions, proximity to critical normal organs, tumor shrinkage and dramatic weight loss) are all key factors in this evaluation. As such, we seek to enroll a sufficiently large series of diverse patients in each stratum. This pilot study will enroll 30 patients per stratum in approximately 1 year (e.g., NSCLC) up to 4 years (e.g., gynecologic cancers), depending on the particular stratum. Once a stratum has enrolled the target number, the study remains open but enrollment to that particular stratum is closed. We expect that the entire study will take approximately 5 years to complete.

10 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 study progress, as well as the construction and implementation of a site data and safety-monitoring plan (see section 13, Study Monitoring, Auditing and Inspecting).

The Medical Monitor will be Daniel Pryma, 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. Pryma's background and experience he is an appropriate Medical Monitor for this study. In the role, he will review all study progress, 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 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 annually. Serious and unexpected issues will be handled on an ad hoc basis through calls or e-mail. Documentation of all communication with the Medical Monitor will be maintained in the study specific Regulatory Binder. Copies of a Medical Monitor report requiring action on the part of the Principal Investigator (PI) to protect subject safety or study integrity will be submitted to the DSMC within 10 business days.

10.1 *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 DSMC audit of this trial will be performed twice a year for as long as the trial remains open for accrual. The principal investigator will be notified in advance of the selection of their protocol for review. Three randomly selected patients or 10% of the total accrual, whichever is higher will be audited. A written report is provided to the principal investigator following this audit. Any rating less than satisfactory would warrant a repeat full review at the time of the next scheduled audit or sooner, depending upon the extent of the deficiencies found. Substantial protocol deviations will be reported to the Director

of the Cancer Center and the Administrative Director of the DSMC for consideration of appropriate administrative action, such as suspending accrual to the protocol.

10.2 *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:

10.2.1 *Eligibility*

Deviations from established eligibility criteria will not be encouraged The IRB will be notified of the planned deviation and a copy of all applicable amended study documents will be sent to the IRB. The planned deviation will 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 will 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.

10.2.2 ***Non-Reportable-*** During the course of a study, there may be times when deviations are minor (i.e. does not affect subject safety or research integrity) and/or are outside of the control of the investigator or research staff (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 other 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 note, note/memo to file or deviation log. Notes/memos/deviation logs should be signed and dated.

10.2.3 *Reporting Deviations/Exceptions*

Reports to the IRB will be done via the Human Subjects Electronic Research Application system (HS-ERA) and reports to the CTSRMC/DSMC will be done via the electronic clinical trials management system, Velos, and email. Reportable deviations must also be sent to the study Medical Monitor.

11 Data Handling and Record Keeping

All patients must have a signed Informed Consent Form and a 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. 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.

HIPAA Compliance: See section 6.1.

11.1 *Data Entry*

All patients must have a signed Informed Consent Form and aconfirmation 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.

Imaging: Copies of all imaging for these studies will be maintained by the Department of Radiology at the University of Pennsylvania.

Follow-up: Follow up visits will occur as per the standard of care. Subjects will be considered off study as of the date of their last radiation treatment.

11.2 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 signed consent form containing the required HIPAA elements 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.

11.2.1 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.).

12 Records Retention

12.1 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.

12.2 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 which 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.

13 Study Monitoring, Auditing, and Inspecting

13.1 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, "A Volume, Motion, and Anatomically Adaptive Approach to Photon and Proton Beam Radiotherapy" is a trial that is subject to oversight of the UPCC through the Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) and the Data Safety Monitoring Committee (DSMC). These oversight committees serve 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 CTSRMC's role is to serve as a rigorous scientific peer review mechanism for all cancer-related non-cooperative group human research studies conducted at the University of Pennsylvania. The Data Safety Monitoring Committee (DSMC) is responsible for overseeing the process of monitoring of studies and the conduct of audits. The clinical trial, "A Volume, Motion, and Anatomically Adaptive Approach to Photon and Proton Beam Radiotherapy" is considered a low-risk study. The investigators on this study are responsible for the continuous, close monitoring of subjects enrolled on this trial.

13.2 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 approximately every 6 months for the duration of the study. The principal investigator will be notified in advance of the selection of their protocol for review. Three randomly selected patients or 10% of the total accrual (up to 10 patients), whichever is higher will be audited. Please note- this schedule may be changed at the
discretion of the DSMC. A written report is provided to the principal investigator following this audit. Any rating less than satisfactory would warrant a repeat full review at the time of the next scheduled audit or sooner, depending upon the extent of the deficiencies found. Substantial protocol deviations will be reported to the Director of the Cancer Center and the Administrative Director of the DSMC for consideration of appropriate administrative action, such as suspending accrual to the protocol.

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

14. 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.

15 Study Finances

15.1 Funding Source

This study is being funded by the Department of Radiation Oncology at UPenn.

16 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 and Principal Investigator. Any investigator involved with this study is obligated to provide the sponsor with complete test results

17.0 REFERENCES

1. Fox, J., E. Ford, et al. (2008). "Quantification of Tumor Volume Changes During Radiotherapy for Non-Small-Cell Lung Cancer." Int J Radiat Oncol Biol Phys.

2. Barker, J. L., Jr., A. S. Garden, et al. (2004). "Quantification of volumetric and geometric changes occurring during fractionated radiotherapy for head-and-neck cancer using an integrated CT/linear accelerator system." Int J Radiat Oncol Biol Phys **59**(4): 960-70.

3. Britton, K. R., G. Starkschall, et al. (2009). "Consequences of anatomic changes and respiratory motion on radiation dose distributions in conformal radiotherapy for locally advanced non-small-cell lung cancer." Int J Radiat Oncol Biol Phys **73**(1): 94-102.

4. Hui, Z., X. Zhang, et al. (2008). "Effects of interfractional motion and anatomic changes on proton therapy dose distribution in lung cancer." Int J Radiat Oncol Biol Phys **72**(5): 1385-95.

5. Vanuytsel LJ, Vansteenkiste JF, Stroobants SG, et al: The impact of (18)F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) lymph node staging on the radiation treatment volumes in patients with non-small cell lung cancer. Radiother Oncol 55:317-24, 2000

6. Harsolia A, Hugo GD, Kestin LL, et al: Dosimetric advantages of four-dimensional adaptive image-guided radiotherapy for lung tumors using online cone-beam computed tomography. Int J Radiat Oncol Biol Phys 70:582-9, 2008

7. Stevens, C. W., R. F. Munden, et al. (2001). "Respiratory-driven lung tumor motion is independent of tumor size, tumor location, and pulmonary function." Int J Radiat Oncol Biol Phys **51**(1): 62-8.

8. Yaremko, B. P., T. M. Guerrero, et al. (2008). "Determination of respiratory motion for distal esophagus cancer using four-dimensional computed tomography." Int J Radiat Oncol Biol Phys **70**(1): 145-53.

9. Zhang, X., K. L. Zhao, et al. (2008). "Four-dimensional computed tomography-based treatment planning for intensity-modulated radiation therapy and proton therapy for distal esophageal cancer." Int J Radiat Oncol Biol Phys **72**(1): 278-87.

10. Bussels, B., L. Goethals, et al. (2003). "Respiration-induced movement of the upper abdominal organs: a pitfall for the three-dimensional conformal radiation treatment of pancreatic cancer." Radiother Oncol **68**(1): 69-74.

11. Nam, H., W. Park, et al. (2007). "The prognostic significance of tumor volume regression during radiotherapy and concurrent chemoradiotherapy for cervical cancer using MRI." Gynecol Oncol **107**(2): 320-5.

12. Lin, A., S. Jabbari, et al. (2005). "Metabolic abnormalities associated with weight loss during chemoirradiation of head-and-neck cancer." Int J Radiat Oncol Biol Phys **63**(5): 1413-8.

13. Milano, M. T., M. C. Garofalo, et al. (2006). "Intensity-modulated radiation therapy in the treatment of gastric cancer: early clinical outcome and dosimetric comparison with conventional techniques." Br J Radiol **79**(942): 497-503.

14. Talamonti, M. S., W. Small, Jr., et al. (2006). "A multi-institutional phase II trial of preoperative full-dose gemcitabine and concurrent radiation for patients with potentially resectable pancreatic carcinoma." Ann Surg Oncol **13**(2): 150-8.