A virtual clinical trial to assess the impact of Dual-Energy CT on plan quality, dose-delivery accuracy, and simulated outcomes of patients treated with proton or photon therapy

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Protocol #: 201711149
Version Date: 10/5/22

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Protocol Revision History

Initial Approval Version	**01/10/2018**
Amendment #1 Version	**06/01/2018**
Amendment #2 Version	**01/25/2019**
Amendment #3 Version	**05/01/2019**
Amendment #4 Version	**05/17/2019**
Amendment #5 Version	**12/16/2020**
Amendment #6 Version	**03/31/2021**
Amendment #7 Version	**06/08/2022**
Amendment #8 Version	**10/05/2022**

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SCHEMA

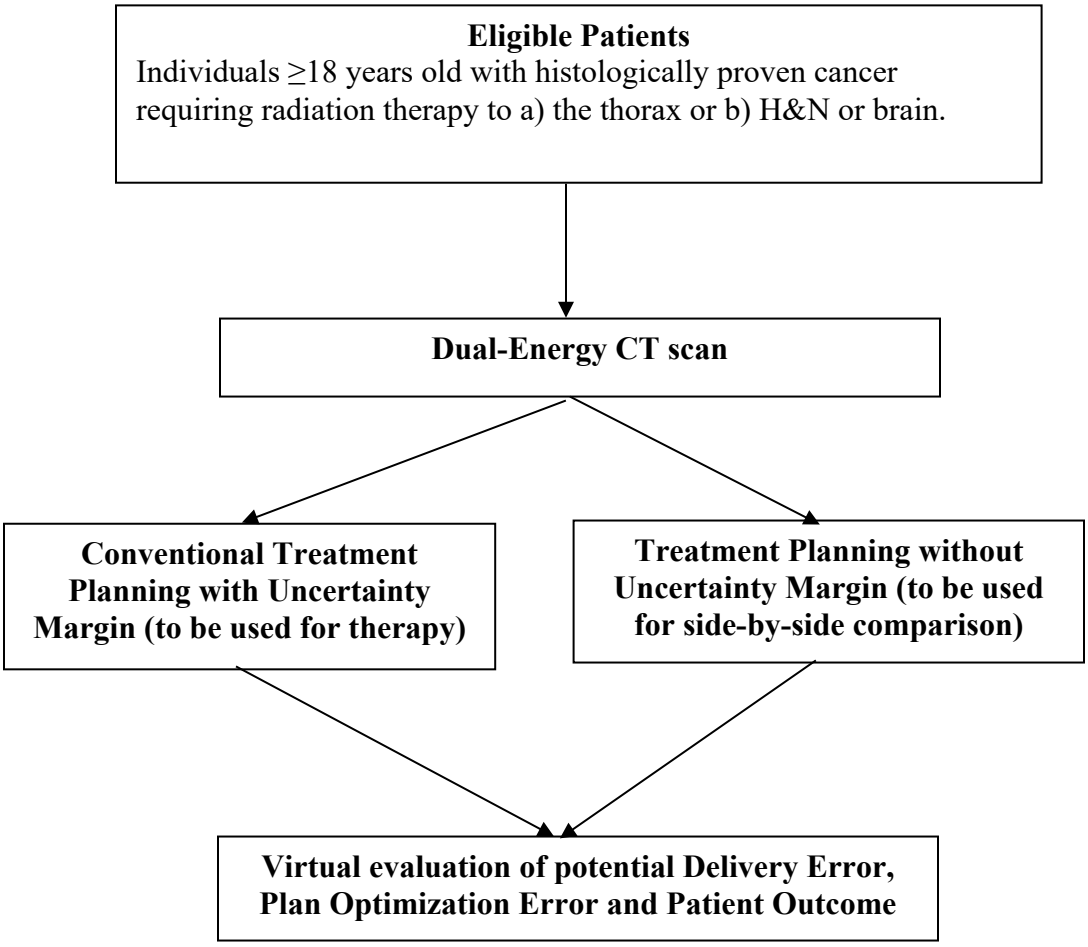

Table of Contents

1.0 BACKGROUND AND RATIONALE

1.1 Proton Beam Therapy

Proton beam therapy (PT) is a rapidly evolving modality with high potential for improving radiation therapy clinical outcomes because of its ability to deliver high doses to the target tissue while sparing surrounding normal tissues. Because of the finite range of protons in tissue, proton dose rapidly peaks at a maximum value (call the "Bragg Peak") near the end of the charged particle range and then abruptly falls to negligible levels. By properly modulating the proton energy, and superposing many Bragg Peaks (the "spread-out Bragg peak" or SOBP), a single-field dose distribution is created which uniformly treats the tumor and falls to negligible levels within a few mm beyond the distal tumor margin, thereby sparing almost completely normal tissues located distal to the tumor. However, PT dose delivery is very sensitive to the physical characteristics of the tissues in the beam's path. Both the magnitude and position of the Bragg peak depends on the composition and density tissue of tissues traversed by the protons. Recommended {ICRU, 1989 #1028; ICRP, 2003 #904} organ/tissue compositions and densities, available for radiotherapy planning, are based upon historic (mostly from 1930-1960) tissue sample measurements{White, 1988 #1030; Woodard, 1986 #1031; Hammerstein, 1979 #1032} with large variations within the suggested values {Brooksby, 2006 #1052; Dance, 1999 #1033; Geise, 1996 #993}. These are potentially imprecise values that may vary significantly from patient-to -patient and within a single patient. Due to the aforementioned uncertainties in tissue composition and density, it is customary to add a 3.5% (about 4 mm for 12 cm range protons) to ensure adequate tumor coverage in the face of these so-called proton range uncertainties. Unfortunately, these safety margins significantly reduce the potential for sparing normal tissue.

Mitigating PT range uncertainties through more accurate characterization of tissue density and composition variability would support of more accurate prediction of dose delivered to the tumor target and adjacent normal tissues. Current PT planning practices rely on standard single-energy CT imaging (SECT) which necessitates 3-6 mm range uncertainty margins{Moyers, 2001 #1843; Zhang, 2007 #1844} that significantly increases exposure of adjacent organs to high doses. In theory, dual-energy CT imaging (DECT) can reduce the range uncertainty problem encountered within PT by non-invasively and more accurately measuring the radiological tissue properties needed to perform accurate PT dose calculations{Yang, 2010 #1853; Williamson, 2006 #923}. However, as currently configured, commercial CT scanners cannot support the level of measurement accuracy required by DECT analysis {Williamson, 2006 #923} to significantly reduce range uncertainty margins .

1.2 Study Rationale

The aim of this protocol is to refine the accuracy of PT by the use of DECT, in conjunction with novel iterative image reconstruction algorithms, to more precisely determine the tissue properties through which the proton beam path travels.

Plan quality in proton therapy is compromised by lack of accurate knowledge of proton stopping power, giving rise to dose prediction errors (DPEs) and optimization-convergence errors (OCEs). The DPEs are defined as the difference between the dose calculated by the treatment planning system and the actual dose delivered to the patient, mainly affected by the inaccurate prediction in the distal edge of a proton beam. OCE is defined as the difference between a clinically executed plan produced by an optimizer based on dosimetric approximations (e.g., SECT) and a better plan (e.g., based on DECT). Accounting for inaccuracies or uncertainty in proton stopping power, the planning optimizer must include a safety margin for the resulting range uncertainty and perform robust optimization using the distribution of errors. We hypothesize that both DPEs and OCEs arising from SECT SP mapping errors will give rise to measurable changes in clinical outcomes and that this loss of clinical efficacy can be reduced with more accurate estimation of proton stopping power using DECT.

Knowledge gained from the DECT will be used to generate a mock PT plan for comparison purposes. Successful completion of this project is intended to measure potential increases in the accuracy with which cancers can be treated with proton therapy and to reduce the potential incidence of normal tissue toxicity. We will then evaluate whether the additional normal tissue dose sparing achieved in these mock plans could improve outcomes for patients undergoing proton therapy by reducing normal tissue complications or enabling tumor dose escalation in comparison to the more traditional 3-6 mm estimates of range uncertainty from Moyer et al.

Uncertainty in proton range is incorporated into proton plan optimization in two ways: safety margin and robust optimization. Safety margin involves expanding CTV and OAR contours (generally by 3.5% of proton range) as recommended by ICRU 50 and 62. Recent studies have demonstrated that robust optimization in proton therapy produces more consistent and predictable dose distribution through the whole treatment course. Given the PDFs describing various uncertainties (setup, organ motion, and true vs. apparent SPR values), robust optimization selects multiple worst case scenarios (instances of patient anatomy and SPR assignments) from the ensemble of all possible instances described by the PDFs. The optimizer then optimizes the plan to satisfy the planning constraints and goals simultaneously on the multiple worst-case scenarios. The resultant plan is robust in the sense that acceptable outcomes will be realized even in the face of the most unfavorable random outcomes (positioning and SPR errors) that are likely to occur. In clinical practice, volumetric imaging greatly reduces the uncertainty associated with setup and sheds light on pre-treatment reoptimization of the treatment plan. As the range uncertainty becomes the largest uncertainty in plan optimization, accurate information on proton stopping power helps the optimizer achieve a more optimal plan.

Patient participation will be limited to having a DECT instead of the standard SECT. That single DECT session will be used to generate two treatment plans; one using standard range uncertainty margins and the second using exact measures of tissue density from the DECT to generate a mock treatment plan for comparison. We expect that the mock treatment plan will have tighter margins around the tumor and spare more normal tissue. Eligible patients

will either have lung cancer or cancer of the brain or base of skull. We have chosen these two patient populations because the tumor is adjacent to air densities where range uncertainty is greater, the problem poses the greatest technical challenge, and reducing the projected toxicity to critical structures would be clinically most meaningful (i.e. reducing dose to the esophagus or optic nerve).

Application of novel CT imaging systems to human patients will allow their performance to be evaluated in a clinical context in ways that cannot be duplicated in phantoms or non-human models. By using human subjects, this research proposal is able to investigate the accuracy of dual-energy CT in the calculation of SPRs that significantly affect the outcome of patients treated with proton therapy.

1.3 CT scanning equipment

State-of-the art commercially marketed CT simulators in the Department of Radiation Oncology will be used to acquire the research data needed for these projects. Currently, the systems available to this project include the Philips Brilliance Big Bore CT/simulator (16 detector rows and 85 cm bore) and the Siemens Confidence CT/simulator (20 detector rows and 80 cm bore).
In addition to acquiring medically-routine CT datasets, each patient subject will be scanned sequentially at two or three different beam energies (80 or 90 kVp, 100 kVp, 120 kVp, and/or 140 kVp) as part of this research study. These additional scans will be acquired utilizing the FDA-approved workflow and scanner operating modes. Sinogram data will be exported in raw, minimally processed form utilizing proprietary data export and processing tools provided to the investigators by the scanner vendors. In no case, will the additional local imaging dose (in terms of $CTDI_{vol}$) given to the patients by the two or three additional scans exceed 6 cGy per session.

1.4 Investigational image reconstruction algorithms and radiological quantity modeling tools

The overall goals of the grant application (1R01CA212638, "Q*uantitative Dual-energy CT Imaging for Cancer Imaging and Radiation Therapy Applications*"), is to develop, validate and implement in clinically useful forms novel iterative dual-energy x-ray CT image reconstruction algorithms which incorporate realistic models of CT data acquisition physics, including beam hardening, scatter, detector response, and measurement noise. Our promising preliminary results demonstrate tissue cross section maps that are more accurate and have lower uncertainty than either post-reconstruction dual-energy CT mapping processes or state-of-the-art single-energy stoichiometric tissue property mapping. The connection between CT measurements and image intensity and PT-relevant radiological quantities is mediated by another innovation, the basis vector model (BVM) {Han, 2016}.

Immediately following acquisition of sequential dual energy images from patient subjects, raw sinograms without beam-hardening or scatter corrections will be extracted with the vendor's support, in addition to vendor reconstructed images and preprocessed sinograms. The raw sinogram data will serve as input to the novel iterative DECT image reconstruction software.

2.0 OBJECTIVES

2.1 Primary Objectives

To evaluate 3D organ- and patient-specific distributions of various radiological quantities, including proton stopping powers.

2.2 Exploratory Objectives

To assess the impact of DECT tissue property mapping on
a.) plan quality
b.) dose-delivery accuracy, and
c.) simulated patient outcomes
for locally advanced lung, H&N and brain tumor patients treated with proton therapy.

3.0 PATIENT SELECTION

1. Diagnosis of histologically proven primary or metastatic cancer requiring thoracic radiation therapy OR radiation therapy to the H&N or brain.
2. At least 18 years of age.
3. Planning to undergo proton- or photon-beam radiation therapy as part of the clinical management of the diagnosed cancer.
4. No implanted metallic objects excepting dental prostheses in the region to be scanned.
5. No IV or oral contrast medium within 24 hours prior to DECT image acquisition.
6. Not pregnant.
7. Able to understand and willing to sign an IRB-approved written informed consent document.

3.1 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

5.0 STUDY PLAN

5.1 Experimental procedures and data to be acquired

Patient therapy will not be affected by enrollment in this study. Patients enrolling in this study will undergo additional sequential DECT scans in addition to their routine SECT or DECT scans by enrolling in this study, which will increase imaging dose to the patients. An additional two sequential scans of the thorax or H&N/brain will be acquired at scan settings ranging from 70kVp to 140 kVp (with or without additional filter) prior to initiating RT. Typically, the experimental DECT imaging data will be acquired prior to the clinically-necessary CT simulation study in the same session. Up to two additional experimental DECT imaging sessions should be scheduled when logistically feasible. For example, if a patient subject requires re-simulation, DECT scan data should be acquired prior to the clinical simulation study in the same session. Raw sinograms without beam-hardening or scatter corrections will be exported from the scanner and archived with the vendor's support. In addition, clinical SECT and DECT images acquired as part of routine RT planning will be collected for this study. For H&N and brain patients, the DECT scan volume should extend from the superior-most aspect of the cranium down to the suprasternal notch. For the thoracic patients, the scan volume should encompass the entire lung parenchyma (apices to base).

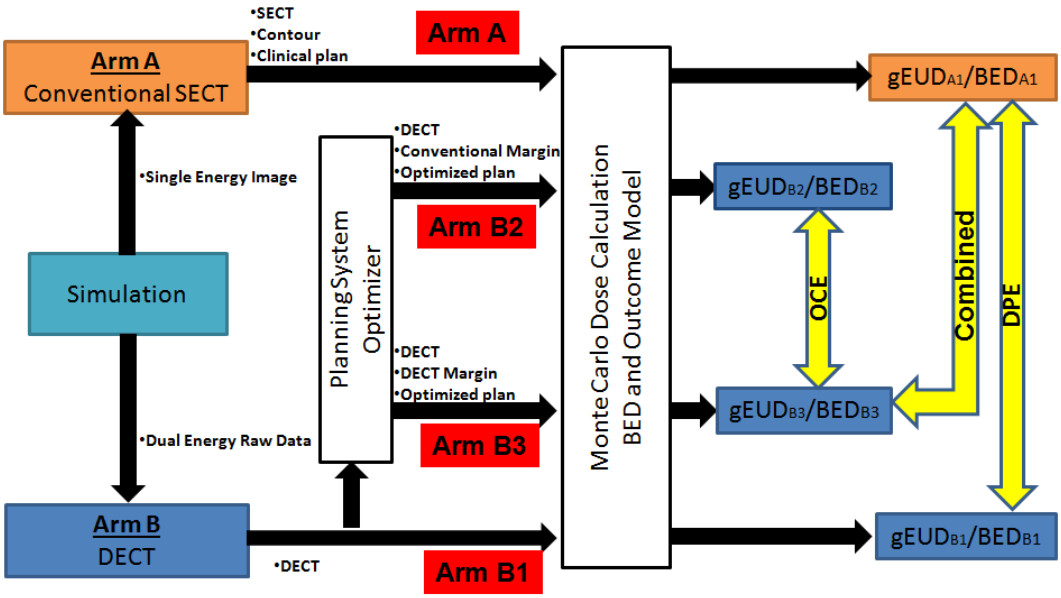

Figure 1: Anatomy of a virtual clinical trial illustrating its two main components: a planning and delivery module that uses single energy CT reconstruction (SECT) for proton stopping power; and a module for estimating the dose actually delivered by the proposed dual energy CT (DECT) reconstruction for proton stopping power. In addition to comparing dose volume histogram (DVH) metrics as clinical outcome surrogates, outcome models such as generalized equivalent dose (gEUD) will be used.

5.2 Study endpoints and methods of analysis

5.2.1 Definition of Virtual Clinical Trial

Figure 1 illustrates the concept of virtual clinical trial (VCT), a relatively new method in radiotherapy to evaluate the impact of a new technology with greatly reduced cost and risk to participating institutes and patients. The trial takes full advantage of computer modeling and simulation to evaluate the benefits of proposed technology in patient outcomes. In essence, the collected research images serve as an *in silico* model of the patient. On each patient, the impact of various planning and image reconstruction strategies can be assessed over the patient population.

5.2.2 Dose Evaluation Schema

We will perform a VCT for each tumor site to assess quantitatively dose prediction errors (DPEs) and optimization-convergence errors (OCEs) associated with more approximate SECT stopping power mapping. In the VCT, every patient will go through the current clinical workflow for planning and dose delivery, where SECT is the primary image for treatment planning and conventional range uncertainty of 3.5% is employed. The SECT data uses one of the two DECT data sets. The DECT images will be used differently in Arm A and Arm B of the VCT.

In Arm A, patients are treated with treatment plans optimized and calculated on the SECT data. Plan dose is re-calculated for every patient with the clinical plan in a Monte Carlo dose calculation engine for better accuracy. We will use TOPAS, an extension of Geant4 simulation toolkit, as the dose calculation engine.

In Arm B, the DECT data is used for plan optimization and dose calculation. In Arm B1, DECT data is used to estimate the actual dose delivered using the clinical plan based on SECT data. In Arm B2, the plan is re-optimized on DECT data with the conventional uncertainty margin of 3.5% of proton range. In Arm B3, the plan is re-optimized on DECT data with the SPR uncertainties derived from the patient-specific uncertainty model developed.

5.2.3 Definitions

DPE. The fractional DPE is $(D_{\mathbf{x}}^{DE,B1} - D_{\mathbf{x}}^{SE,A})/D_{\mathbf{x}}^{DE,B1}$, based on the difference in planned dose (Arm A) and delivered dose (Arm B1), where x is the dose-volume index and the superscript A and B1 denotes the dose plan from Arm A and B1 respectively.

OCE. The fractional OCE is $(D_{\mathbf{x}}^{DE,B2} - D_{\mathbf{x}}^{DE,B3})/D_{\mathbf{x}}^{DE,B2}$, based on the difference in planned dose optimized on DECT with the conventional uncertainty margin (Arm B2) and the SPR uncertainties derived from the patient-specific uncertainty model developed in Arm B3.

Combined. The total change in dose between optimized plans from SECT and DECT data.

5.3 Modeling of clinical impact

In order to quantify the reduction of DPEs and OCEs in clinically relevant terms and to resolve ambiguities associated with purely dosimetric outcome indices, radiobiological isoeffect models and outcome prediction models will be used. To account for local delivery variations (dose rate, fraction size, linear energy transfer) in relation to local radiosensitivity, we will use the isoeffective quantity, biologically effective dose or BED, derived from the linear-quadratic (LQ) model. LQ parameters from photon therapy clinical data will be adapted to account for the fact that linear energy transfer varies along the proton path, producing variations in relative biological effectiveness (RBE) which is maximized near each pristine Bragg peak. As higher linear energy transfer (LET) produces more single-and double-strand breaks, tissues near the distal SOBP act more like early responding tissues with higher α/β compared to photon treatments. Assuming a first-order approximation for the dependence of the proton αp parameter on LET (evaluated by TOPAS), it can be approximated by $\alpha p=\alpha x+\chi\alpha x/\beta x \bullet LET$, where αx and βx are photon therapy LQ parameters. We found χ to be 0.0079 μm keV-1 Gy-2 from fitting the experiment data20 to proton therapy. BED, rather than physical absorbed dose, will be used as a dose accumulation parameter, giving rise to BED volume-histograms.

Outcome models take this process one step further by transforming a complex 3D dose distribution into a single number that is a surrogate for a clinically measurable endpoint. Equivalent uniform dose (EUD) was introduced by Niemierko in 1997 as the primary surrogate for tumor control probability (TCP). For quantifying normal tissue responses, we use Mohan's approach, which reduces the cumulative BED volume histogram to a single equivalent dose using generalized EUD (gEUD) and applies the LKB model to compute the normal tissue complication probability (NTCP).

We will quantify difference in tumor control and normal tissue complications between VCT trial arms A and B for each relevant tumor and normal-tissue endpoints. For brain, the complication endpoints to be reviewed include brainstem injury, panophthalmitis/blindness and brain necrosis; for lung, the complication endpoints to be reviewed include esophagitis, pneumonitis, and cardiac morbidity.

6.0 SAFETY MONITORING AND REPORTING

6.1 Potential Risk

In addition to potential loss of privacy, the delivery of small additional doses of ionizing radiation associated the additional DECT research scans poses a small risk of carcinogenesis to patient subjects. The total additional radiation dose for the dual-energy data acquisition will be less than 6 cGy per imaging session, or a total of no more than 24 cGy over the entire treatment course. The potential risk of cancer death due to this modest additional dose of ionizing radiation is theoretical and acknowledged to be uncertain. It is estimated that there is a 0.0002 incidence of increased cancers, over a risk period of 30 years, per 1 cGy radiation. No contrast media or other invasive procedures will be required.

6.2 Protection against Risk

The potential risk of increased radiation exposure due to increased imaging is currently only known from theoretical analyses. It is estimated that there is a 0.0002 incidence of increased cancers, over a risk period of 30 years, per 1 cGy radiation. This small radiation dose will be overwhelmed by therapeutic doses (30-90 Gy) administered to the region being imaged. There are no study-related limitations on patient care. No subjects will be enrolled prior to IRB approval. The imaging systems to be used are all FDA approved devices. The risk to patient privacy will be mitigated by anonymizing the images and raw datasets, so that patient identity is known only to the protocol PI and data managers, prior to processing the data.

6.3 Potential Benefits of the Proposed Research to the Subjects and Others

The protocols of this project will not alter the participating subject's therapy beyond the limits specified in the eligibility requirements and protocol conduct. In particular, these protocols place no limits on the use of the acquired imaging data to manage the patient's radiation therapy. The treating radiation oncologists may use this imaging data and its results to improve the participating subject's therapy, provided that all applicable FDA and IRB guidelines are followed. Beyond this possibility, no direct benefit to the patient is expected. The alternative is not to participate in the study.

The overall hypothesis of this study is that dual-energy CT imaging, when coupled with appropriate image reconstruction and analysis techniques, can be used to accurately map the radiological properties (total, scattering, and photoelectric cross sections; stopping power ratios and multiple-scattering cross sections) of human tissue on a voxel-by-voxel basis. Moreover the data will provide preliminary data to design a broader trial to assess the hypothesis that cross-section imaging significantly improves dose delivery accuracy. This will increase the accuracy with which cancers can be treated with charged particle radiation therapy and reduce the incidence of normal tissue toxicity. The additional normal-tissue dose sparing may improve outcomes to future patients undergoing treatment by reducing normal tissue complications or enabling tumor dose escalation.

6.4 Adverse Events

There are no anticipated study-related adverse events, aside from those listed in the Potential Risks section (above). All unanticipated adverse events will be reported to the IRB, as required within 10 days of notification. All serious unanticipated adverse events will be reported within 24 hours.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting.

6.5 Data and Safety Monitoring Plan

The study principal investigator and study coordinator will monitor for breaches of confidentiality and other adverse events on an ongoing basis. Once the PI or study coordinator becomes aware of a reportable adverse event, the event will be reported to HRPO and QASMC according to institutional guidelines. This study does not require QASMC audit or submission of DSM reports.

7.0 STATISTICAL CONSIDERATIONS

Based on the differences and patient-to-patient variability from our preliminary data, recruiting 20-25 patients for each site (depending on DVH endpoint) is sufficient to detect 2%-3% changes in absolute DVH surrogates, e.g., 2% changes in heart V30 for 20 NSCLC patients, with 80% power at 95% level of confidence from reducing range uncertainty from 3.5% to 1.0%. Because each patient subject is their own control, we assumed a moderate positive correlation between treatment arms of 0.5, consistent with that observed in other image-guided radiation therapy VCTs40. For lung cancer, we hypothesize that we will observe >40% reductions in esophageal V60 (corresponding to reduction of ≥g2 esophagitis from 60% to 39% (71), a reduction >30% in mean heart dose (from 8 Gy70 to 5 Gy, reducing relative risk factor for late cardiac disease from 1.60 to 1.3727, and total lung V20 from 15% to 10% (lowering risk of radiation pneumonitis from 15% to 8%48). Likewise, greater precision towards predicting radiation dose to neighboring neural structures such as the optic chasm, optic nerve, brainstem, and eye is clearly important. Tumor volumes frequently abut these structures, creating situations where the physician chooses to underdose the tumor target, rather than risk severe toxicity in normal tissue resulting in complications such as blindness.

The hypothesis to be tested is that Monte Carlo treatment plans based upon standard of practice single-energy CT cross-section mapping differ significantly from Monte Carlo plans using cross-section maps derived from our proposed quantitative dual-energy CT (DECT) imaging methodology. Neither the expected magnitude of the difference nor its variability is known. However, from the literature and our preliminary studies, a minimum of 10%-15% difference might be considered clinically significant and the standard deviation of the difference is expected to be about 15%. Using a paired t-test, a sample size n=20 per group would enable us to detect differences of 15% and 12% for percent standard deviations of 15% and 10%, respectively, with 80% power at the 5% significance level. If we relax the significance requirement to 10% (appropriate for a preliminary/exploratory study), differences of 13% and 8.5% will be detectable under these conditions.