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DMH-Based Plan Evaluation and Inverse Optimization in Radiotherapy

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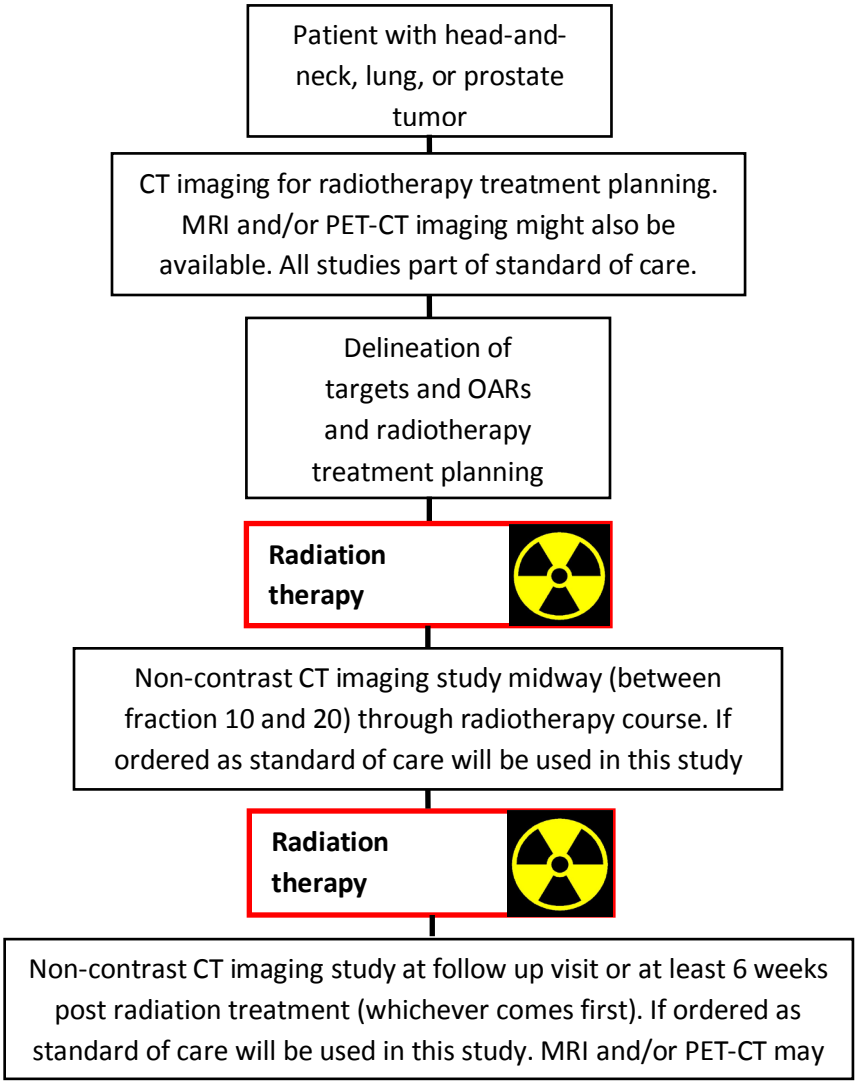
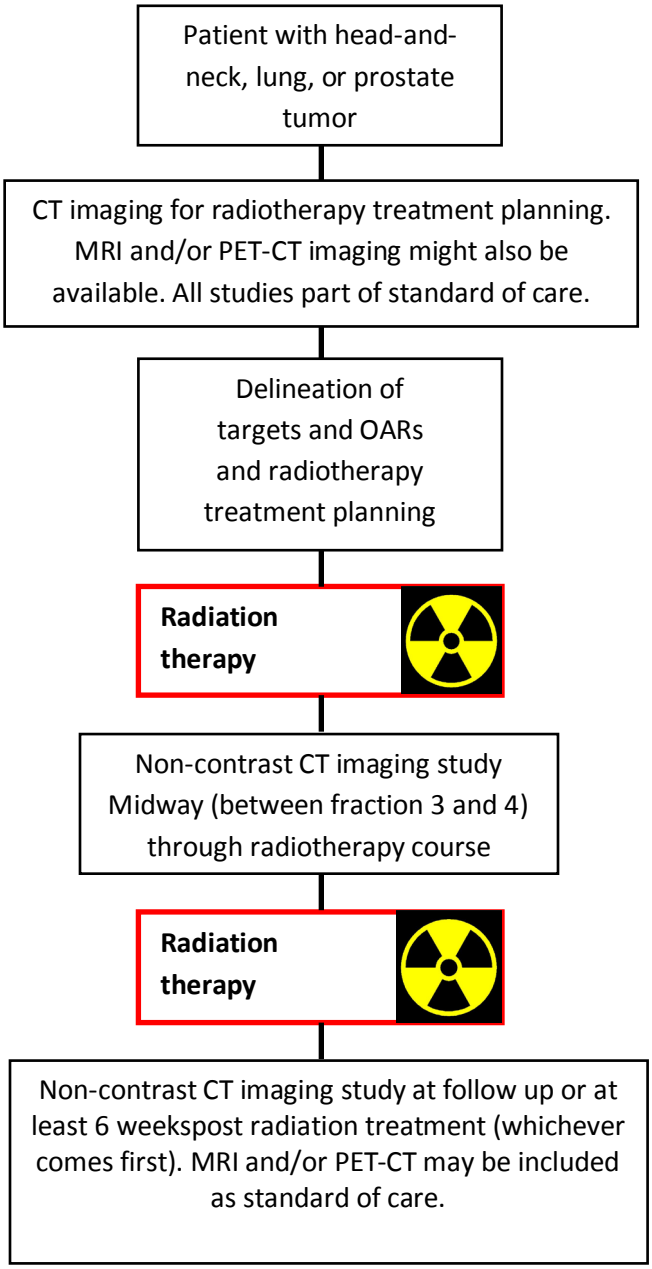
SCHEMA 3DCT, IMRT, VMAT:



CT = computed tomography; MRI = magnetic resonance imaging; PET-CT = positron emission tomography; 3DCT = three-dimensional conformal radiotherapy; IMRT= Intensity Modulated Radiotherapy; VMAT = Volumetric Modulated Arc Therapy; CT = Computed Tomography Imaging; OARs = Organs at Risk;

SCHEMA SBRT:



SBRT = Stereotactic Body Radiotherapy; CT = Computed Tomography Imaging; OARs = Organs at Risk;

HYPOTHESES:

- Mass-based inverse optimization in radiotherapy treatment planning will result in a reduction of normal tissue and organs at risk (OAR) doses for desired prescription therapeutic doses to the targets.
- Dose-mass histograms (DMHs) may be more relevant to radiotherapy treatment planning and treatment plan assessment than the standard of care, realized through dose-volume histograms (DVHs)

1.0 BACKGROUND

1.1 Study Disease

Lung cancer is the third most commonly occurring non-cutaneous cancer in the USA where the estimated number of new cases in 2013 was 228,190. Worldwide, it is the leading cancer in both incidence (1.61 million new cases annually) and mortality, (1.35 million deaths annually). In the USA alone lung cancer kills approximately 160,000 individuals yearly – more people than breast, colon and prostate cancers combined.[1-3] The 5-year actuarial survival estimate for non-small cell lung cancer (NSCLC) is approximately 15% for stages III-IV, and better for stages I-II. It has been shown that local disease control, using conventionally fractionated dose regimens, has not improved in more than a decade.[4-14]

Approximately 53,000 new cases of head and neck cancers [mostly squamous cell carcinoma (HNSCC)] are diagnosed in the United States each year. About two thirds of those cases present with a locally advanced disease. HNSCC patients comprise another challenging therapeutic category.[15-28]

Prostate cancer is the most commonly occurring non-cutaneous cancer in the USA with a reported incidence of about 238,000 new cases each year. Despite advances in early diagnosis and in treatment, its cure remains elusive. Local persistence of prostate cancer treated with radiation therapy is under-appreciated. Prostate cancer has a long natural history and persistent disease may not be realized for many years.[29-38]

1.2 Rationale

1.2.1 Standard of Care in Radiotherapy

Lung cancer is the most common cause of cancer-related deaths. The prevalent histological types are non-small cell (NSCLC) and small-cell (SCLC) lung carcinomas. Treatment options include surgery, chemotherapy, and radiotherapy. It has been demonstrated that radiotherapy dose of 70 Gy is a significant threshold in terms of survival benefits for NSCLC, while doses of ~85 Gy are required to achieve 30 months of local progression-free survival. Phase I RTOG 0117 trial demonstrated that 74 Gy is the maximum tolerated dose in combined chemo-radiotherapy for that disease, indicating the detrimental effects of chemoradiotherapy which prohibit dose escalation. Single institution studies have reported on an improved local control with higher dose levels and/or higher doses per fraction, indicating that patients might benefit from radiotherapy dose escalation, realized by treatment planning and/or delivery techniques which minimize radiation doses to surrounding anatomical organs. In other words, if a technique which minimizes radiation dose to healthy tissue is developed, it will allow dose escalation (not to exceed an accepted level of healthy tissue toxicity) which might improve patient outcomes. Healthy tissue tolerance is very often the dose limiting factor for a successful definitive treatment. Symptomatic radiation-induced lung injury (RILI) occurs in ~30% of the patients, while radiologic evidence for RILI occurs in ~50% of the NSCLC cases. Radiographic changes in lung (as function of regional dose) have almost linear relation with dose across the therapeutic range. Lung toxicity has been correlated with both mean lung dose (MLD) and local doses. Published data indicates that the rate of radiation pneumonitis (RP) is dependent on MLD and volume indices ranging from V5 to V30. The abovementioned data suggest that new strategies for a potential dose escalation, through innovative treatment planning and delivery techniques, where lower radiation doses are delivered to healthy tissue, need to be explored.[10, 12, 14, 34, 39-91]

Another challenging group of cancer patients includes head-and-neck squamous cell carcinoma (HNSCC) cases. Radiotherapy combined with concurrent chemotherapy is commonly used for treatment of stages III-IV of these cancers (category 1 level of evidence in the recommendations of the National Comprehensive Cancer Network Head and Neck Pane). Although various meta-analyses have clearly shown that delivering chemotherapy and radiotherapy concomitantly (chemoradiation) significantly boosts the effects of radiation alone, this approach raises a number of practical challenges, most of them resulting from poor treatment tolerance and reduced compliance to the prescribed dose levels of chemoradiation. Most HNSCC patients, receiving high-dose radiotherapy, are affected by severe acute side effects, including mucositis (stomatitis), dysphagia, and skin toxicity (radiation dermatitis). Chemoradiation is

associated with an even higher incidence of severe (grade 3/4) acute adverse events, indicating again the detrimental effects of chemo-radiotherapy combination for this treatment site. Although it has been repeatedly substantiated that combining radiotherapy with cisplatin and sometimes 5-FU yielded the best overall survival data, it can be claimed that the therapeutic potential of these drugs has been taken to its limit. An important avenue of research refers to advances in radiotherapy planning and delivery and, in particular, intensity-modulated radiotherapy (IMRT). Compared with conventional techniques IMRT allows better sparing of unaffected tissues. The subsequent reduction in radiation-induced mucositis and xerostomia may help to decrease the morbidity of intensive concomitant chemoradiotherapy.[16, 17, 19, 20, 22-25, 92-98]

Radical prostatectomy and radiotherapy are both viable treatment options for clinically localized prostate cancer. Both modalities have evolved over time, such that to maximize cancer-free survival, while minimizing health-related risks like urinary incontinence, bowel incontinence, and sexual dysfunction. However, to date there is still not one superior single treatment that is devoid of side effects. Notably, three recent randomized trials have shown a consistent improvement in biochemical failure when adjuvant radiotherapy is administered with prostatectomy. However, the price to be paid for the increased control is the increased risk for complications and side effects in the radiotherapy arm by a factor of two. Over the past decade, many publications have shown that high dose IMRT represents optimal form of external beam radiotherapy for localized prostate cancer. The combination of IMRT with image guidance has allowed an enhanced target precision together with the accompanying reduction in clinical target volumes and even perhaps reduction in the treatment related toxicity. Therefore, development and incorporation into clinical practices of novel advanced radiotherapy planning and delivery techniques will permit us to deliver radiation more safely and reduce treatment duration significantly for thousands of patients.[29-33, 36, 38, 99-118]

Approximately 60% of all cancer patients require radiotherapy for local tumor control. Quite often radiotherapy is combined with other treatment modalities such as chemotherapy. The current state of the art radiotherapy treatment planning and treatment plan evaluation relies on the DVH paradigm, where doses to volumes of target and normal anatomical structures are employed. Recently however, it has been argued that the effects of delivered radiotherapy dose seem to be more closely related to healthy tissue toxicity (and thereby to clinical outcomes) when dose-mass-histograms (DMHs) are considered in treatment plan evaluation.[119-121] So far, mass information has been utilized only

in evaluation of treatment plans and radiobiological modeling for NSCLC. DMHs were introduced for evaluation and review of thoracic treatment plans. Shortly thereafter, the analytic rationale for their application was outlined. Investigation of the difference between DVHs and DMHs and their effects on the treatment outcomes showed that the deviation range between them is large. It was concluded that "*the effectiveness of the dose distribution delivered to the patients seems to be more closely related to the radiation effects when using the DMH concept*". An example figure from Mavroidis *et. al.*, elucidating the grounds for that statement, is presented below.

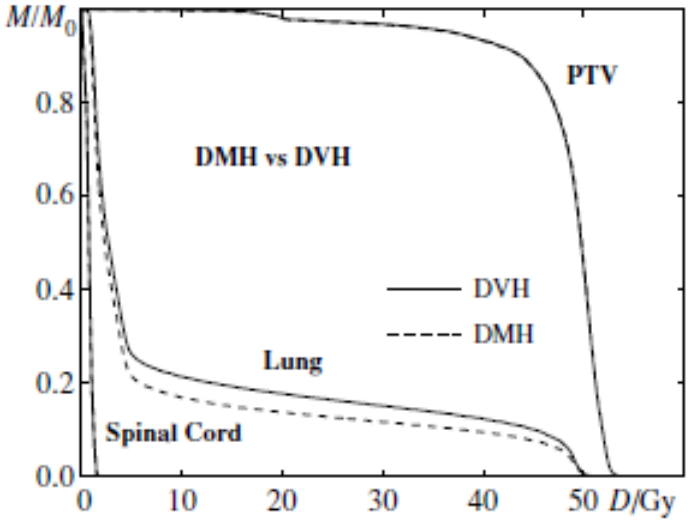


Figure 3. The mean cumulative dose–volume histograms of the PTV and spinal cord show that the difference between the DVH and DMH is negligible. However, the difference of the two concepts appears to be significantly large for the lung.

The figure presents DVH and DMH analyses for a breast patient treated with radiotherapy. The authors state that "*It is shown that the DMH is lower than the corresponding DVH meaning that the lung actually receives a lower dose than what the DVH indicates. By interpreting these figures in terms of tissue response, it was found that the probability for lung complications was changed by 30% of its initial value* ***closer to the clinically observed response rate***"

To date no investigation utilizing tissue mass (or density) effects explicitly in IMRT optimization process has been undertaken. We have incorporatd mass directly in the cost functions for inverse planning, and will study its potential for doses reduction to healthy tissue and the magnitude of the potentially achievable isotoxic dose escalation. For the first time tissue mass information is used for

treatment planning purposes, rather than academic plan review: that is, a shift from DVH- to a new, DMH-based, treatment planning paradigm. We will also look into the use of tissue density incorporation in the cost function, and optimize dose to density rather than dose to volume. Furthermore, we will study global energy minimization (as a fundamental physical principal) and its place in inverse optimization, since it can be readily incorporated in the development of the proposed novel treatment planning framework. From a conceptual stand point there is no difference between mass-based and volume based optimization cost functions when media with constant density is considered. However, human body comprises many different tissues which vastly differ in density, from air cavities to bones. Under those conditions the mathematical representation of the mass-based optimization is more general than the representation of volume-based optimization. In other words, volume-based optimization is a special case of mass-based optimization in a media with a constant density. Therefore, we hypothesize, that applying the more general model (utilized through mass-based optimization) will be advantageous in certain situations and we want to explore what those situations are.[32, 33, 42, 67, 73, 119-126]

1.2.2. Volumetric Imaging for Radiotherapy

All patients receiving radiation therapy undergo a high resolution CT scan, which is a fundamental step in the current clinical radiotherapy planning process. Recently it has become a standard of care to also include complementary imaging modalities such as magnetic resonance imaging (MRI) and/or positron emission tomography (PET-CT), which helps delineate tumors and normal tissue. In addition, it has become quite common to perform MRI and/or PET-CT studies on follow-up visits after radiotherapy course completion in order to assess treatment outcome.

1.2.3. Treatment Planning for Radiotherapy

Cancer patients are treated according to the standard of care with either conformal radiotherapy (3DCRT), intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), or a linear accelerator (linac) based stereotactic radiation therapy (SRT). Treatment planning is performed with any combination of coplanar or non-coplanar fields to deliver the prescribed dose, while restricting the dose to the normal tissues to empirically determined dose levels. Field arrangements and plan parameter optimization are determined by

experienced planners to produce the optimal plan in accordance with volume definitions and attending physician prescriptions and goals.[86, 127-137]

1.3 Gender and Ethnicity

It is estimated that the patient population who received radiation therapy at UMHC between 01/01/2003 and 12/31/2012 consists of 46% White, 10% African American, 42% Hispanic, and 2% Other.

2.0 STUDY OBJECTIVES

2.1 Primary objectives

- To study and evaluate whether DMHs are better suited for predicting radiotherapy response and/or complication (toxicity) than standard of care realized through DVHs.
- To investigate the time-trending changes between patient anatomy and DMH inverse radiotherapy optimization.

2.2 Secondary objectives

- To develop the conceptual framework for mass-based objective functions for inverse planning optimization of radiotherapy treatments.
- To study different forms of mass-based objective functions.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

- Patients must have histologically confirmed head-and-neck, lung, or prostate tumors.
- Patients who will be treated with radiation therapy or concurrent chemoradiation therapy.
- Gross Tumor Volume (GTV) or resection cavity must be visible on CT such that it can be delineated as a target for radiotherapy.
- Patients who are able to understand the investigational nature of this study and agree to sign a written informed consent document.

3.2 Exclusion Criteria

- Pregnant or nursing women will not participate. Women of reproductive potential must be offered a pre-treatment pregnancy test and informed of the need to practice an effective contraceptive method during the therapy.
- Patients younger than 18 years.
- Patients whose size and weight would not allow CT scanning.

No vulnerable populations (fetuses, pregnant women, children, prisoners) will be included in this study.

3.3 Enrollment and Withdrawal

3.3.1 Enrollment Guidelines

Study enrollment, as used in this protocol, will be defined as the investigator's confirmation of the subject's eligibility by signing an eligibility checklist.

3.3.2 Withdrawal Guidelines

Patients can withdraw at any time if they decide to do so. If, for any reason, the attending radiation oncologist decides that patient participation in the study is not in their best interest the subject will be withdrawn from the study. Furthermore, if the PI decides to discontinue the study, subjects' participation will end. Patients who are enrolled on study but not treated will be excluded from all analyses.

4.0 RESEARCH PLAN

To support both currently planned and future investigations, a patient database will be established to manage the CT imaging data acquired through this protocol as well as other relevant data such as MRI and\or PET-CT studies. All analyses in this study will be based on this database.

4.1 Assessment of Protocol Eligibility and Enrollment

Eligible patients will be pre-screened by the attending physicians. If the patient is deemed suitable, informed consent will then be obtained.

4.2 Treatment Planning for Therapy Purposes

This protocol is a non-therapeutic protocol. Therefore, patients enrolled in this protocol will be treated according to the standard of care for IMRT, VMAT, and SRT.[29, 97, 138-144] Treatment planning will be performed with any combination of coplanar or non-coplanar IMRT fields or VMAT fields, to deliver the specified dose while restricting the dose to the normal tissues. Field arrangements will be determined to produce the optimal plan in accordance with volume definitions. The treatment plan used for each patient will be based on analyses of the volumetric dose, including DVH analyses of the planning target volumes (PTVs) and critical normal structures, as well as evaluation of isodose curves and isodose volumes. In addition to the abovementioned analyses (which is according current standard of care) our study will evaluate the pertinent DMHs and isomass volumes for all anatomical structures of interest.

In addition to the planning CT scan and/or pre- and post-treatment MRIs and/or PET-CTs done routinely as part of standard of care, patients enrolled in this protocol will undergo two additional CT imaging studies at different times during the treatment course. CT studies are the primary data source for any type of external beam treatment planning. The information gained from the repetitive CT scans will be used to quantify the volumetric and mass changes of soft tissue (e.g. tumor shrinkage). Furthermore, the data will be used to assess the relation among soft tissue changes and radiographic features as well as dose-mass and dose-volume histograms, as well as the time-trends for DVHs and DMHs.

All head-and-neck patients will be immobilized using custom-fabricated thermoplastic face masks affixed to the couch. Lung and prostate patients would be immobilized in body immobilization bags such as Alpha Cradles and vacuum immobilization bags (or vac-bags). Patients will be immobilized in the intended treatment position and imaged with a CT scanner in the same way as for standard 3DCRT and IMRT/VMAT/SRT treatment planning. The final decision for treatment immobilization devices will be left to the discretion of the attending physician.

4.3 CT Exam Specifications

All imaging studies for this protocol will be carried out at our Siemens 16 slice CT scanner in the Department of Radiation Oncology, Sylvester Cancer Center (SCCC)/SCCC_West/Deerfield Beach/new centers at the University of Miami. All subjects enrolled in this study will undergo four high-resolution CT scans. Head-and-neck and prostate patients will undergo three-dimensional (3D) CT scans, while lung patients will undergo time-resolved four-dimensional (4D) CT scans. 4D CT scans

allow capturing of the anatomical changes due to human breathing. These studies are required for thoracic/abdominal cancers since patient's anatomy changes significantly (on the order of 4-5 seconds) during a course of radiation. We will evaluate the effect of these changes on the calculated radiation dose. If applicable, i.e. requested by the attending radiation oncologist for therapeutic purposes according to the standard of care, the CT exam(s) may use the administration of radiocontrast.

Note that if the attending physician orders a CT scan throughout the course of treatment and/or at the follow-up or at least 6 weeks after completion of therapy as a standard of care, this CT imaging would be used in our research instead of exposing the subjects to additional CT scan for the sole purpose of this protocol. If the midway scan or post treatment scan, as ordered by the attending physician, are performed in the Radiology Department we would transfer the imaging data from PACS to our research treatment planning system for the purposes of this research.

4.4 Other Imaging Studies

Complementary to the two additional CT scans proposed in this study all other patient imaging data will also be collected for our analyses. This data is part of the standard of care used in radiotherapy for cancer and they include MRI and PET-CT scans. MRIs and PET-CTs are very often ordered by the attending physicians for pre-treatment purposes, where they help delineate targets and OARs for treatment planning purposes. Furthermore, MRIs and PET-CTs can also be ordered by the treating doctors several weeks post-radiotherapy to assess tumor response, potential complications, and to assess treatment outcome.

4.5 Experimental Virtual Treatment Planning

The CT data acquired under this protocol will also be used for testing and development of our mass-based optimization methods. Those experimental plans will not be used for patient treatments. The plans used for patient treatment would be based on the standard of care described in section 4.3. Prospective data collection of 3D and 4D CT patient scans will be utilized for tallying DVH and DMH end-points and their relation to changes in pulmonary function, as well as studying interaction between tumor time-trending changes and DMH parameters in NSCLC, HNSCC, and prostate cases. All experimental mass-based treatment planning will be necessarily retrospective. Should a finding on one of the repetitive CT scans necessitate a change in plan or medical intervention, this will be at the discretion of the attending physician and will be performed according to the standard of care.

4.6 Duration of Study

Several CT volumetric studies will be performed for each enrolled subject: one before the radiotherapy course for patient treatment planning purposes (as part of the standard of care), one during the radiotherapy treatment course (between fraction 10 and 20 for 3DCT, IMRT or VMAT patients and after fraction 3 for SBRT patients), and one at follow up visit or at least 6 weeks post-radiotherapy treatment(whichever comes first). The acquisition of these imaging data will require approximately 15 additional minutes of the patient time at those visits.

5.0 DOSE MODIFICATIONS

There will be no immediate benefit to the patients from the performed research, since their course of treatment will not be affected by the proposed prospective data collection. However, an exception might occur if during the CT scans throughout the course of treatment a large tumor response (e.g. tumor regression) or normal tissue changes are discovered. Such a finding may prompt a radiotherapy treatment plan adaptation, which will be left at the discretion of the attending physician.

6.0 DATA ANALYSES PLAN

This clinical imaging study will form a database for future research and development of 3D and 4D treatment planning approaches for different anatomical sites treated with radiotherapy. Statistical analyses will be used to assess the differences among standard of care, realized through DVHs, and our newly proposed mass-based optimizations and DMH evaluations. Those statistical analyses are powered to detect clinically significant differences in dosimetry and estimated clinical outcome endpoints between various proposed simulated treatment techniques. Significant changes include:

- Dosimetric: a dose variation between the different treatment planning approaches for normal tissue structures of more than 7%.

- Estimated clinical outcome: a ≥5% variation of normal tissue toxicity using the generalized equivalent uniform dose (gEUD) metric and isoeffect parameters and analyses tools developed by the NCI funded R01 CA163370 research grant.

We will start with the null hypothesis that no difference between the treatment planning approaches is observed for the dosimetric and the estimated clinical outcome endpoints. Since patients are treated according to the standard of care and only their imaging information is used to estimate the potential outcome benefit of the new planning approaches, each patient serves as a control for themselves. Results will therefore be paired. The differences between the standard of care inverse optimization

and the proposed mass-based schemes for tumors will be tested using one-tailed paired *t*-tests, against a hypothesis that ±3% radiation dose differences in the tumors will not have an observable clinical significance The differences between the optimization results on the remaining parameters for all healthy anatomical structures (within the radiation field) will be tested using standard two-tailed *t*-tests with the null hypothesis set to 0%. We anticipate an enrollment period of five years.

7.0 DATA AND SAFETY MONITORING PLAN

This study is a non-therapeutic study. As described in section 8.4 below the risks to the patients are very minimal, given that all of the enrolled individuals will receive radiation therapy as a standard of cancer care. No adverse events are expected within the scope of our work. Therefore, the data safety monitoring for this study would be performed by the PI and the co-investigators. The research team bears responsibility for suspending or terminating this study.

8.0 HUMAN SUBJECTS INSTRUCTIONS

8.1 SUBJECT POPULATION

Data would be utilized from all Department of Radiation Oncology at UM patients >18 year old with histologically proven head-and-neck, lung, and prostate cancers who will be treated with 3DCT, IMRT, VMAT, and SRT.

8.2 RESEARCH MATERIAL

Along with the CT imaging studies and the physical description of the radiotherapy, the following data will be collected as well from each subject:

MRI studies (if any)	Toxicities
PET-CT studies (if any)	Prior Surgery
Age	Tumor location
Performance status	Diagnostic CT/MRI/PET report
Histology	Tumor volume
Disease stage	Medication
Patient weight	Critical structures

All of the data recorded will be entered into a database maintained by the principal investigator. Majority of that data for each patient is part of either our “record and verify” system or UChart. This data includes patient age, performance, histology, disease stage, patient weight, prior surgery, diagnostic report, medication. It will be

transcribed either by the PI or the study staff. For toxicity we will use CTCAE 4.0 grading system (cf. Appendix II). Tumor volume and location as well as volumes and locations for all adjacent healthy anatomical structures within the radiation field would be determined form the radiotherapy treatment plans used for patient therapy.

8.3 RECRUITMENT PLAN

All eligible patients will be informed of the opportunity to participate in this study by the attending radiation oncologist. Eligibility will be determined by a completion of an eligibility checklist. Specific details of the study, including a copy of the informed consent will be provided to all potential subjects. Informed consent can be obtained by the attending radiation oncologist, principal investigator, or study coordinator at initial consult or at any time prior to radiation therapy planning. The patient will have the opportunity to have any questions answered by any of the co-investigators or study staff involved. Subjects must document their consent to participate by signing a written informed consent form that includes HIPAA authorization and has been approved by the University of Miami IRB.

8.4 POTENTIAL RISKS

The CT imaging studies proposed in this study do not subject patients to any therapeutic intervention beyond what is prescribed as part of their routine clinical care. A synopsis of radiation doses from the proposed imaging studies to be delivered to each subject enrolled in this protocol is presented in Table 1. The data outlines the CT imaging dose from a single CT scan. This data is for a 4D CT scan. 4D CT scans deliver more radiation than much more commonly used 3D CT scans. Therefore, the presented dose estimates are effectively for upper dose limits. 4D CT scanning is relevant only for lungs patients. For head-and-neck and prostate patients standard 3D CT protocols will be used. As mentioned above, the 3D CT scans result in somewhat lower radiation doses than those outlined in Table 1.

Table 2 presents the data for cone beam CT (CBCT) and on-board imagers (OBI), used on daily basis for patient positioning and pre-treatment localization. The cumulative doses in the table are calculated for a standard 35 session course of treatment, aiming to deliver radiation dose between 6600 cGy and 7000 cGy (depending on the fractional dose) to the tumor(s). In those 35 treatments there will be 7 CBCTs (once per week), while the remaining 28 treatments will utilize OBI for patient positioning. If a patient undergoes a SRT treatment, then all 3 to 5 fractions (which comprise this treatment) will require the use of CBCT.

The risk to the participants in our prospective CT data collection is very minimal. The therapeutic doses delivered to cancer patients are of the order of 200 cGy in each daily fraction. It is evident from Table 1 that imaging dose of ~4 cGy, delivered through a 4D CT scan, is ~ 2% of that daily dose. Notably, 2% daily variation in the radiation output is within the operational specifications of modern linear accelerators. In other words the added imaging dose per one CT scan will be no larger than the stochastic variation of the daily machine output. Furthermore, Table 2 demonstrates that the dose resulting from 7 CBCT and 28 OBI applications, used as standard of care for accurate patient daily localization, is equivalent to four 4D CT studies, i.e. one more study that the proposed number in this protocol (we will subject patients to one CT which is standard of care and two more for research purposes).

In summary, the addition of three 3D or 4D CT scans in our prospective data collection will have a negligible dosimetric effect on the patients, given that it is only 6% of a single fractional (daily) dose, or less than 0.2% of the total prescription dose over the course of treatment comprised by 35 fractions.

Table 1: Radiation Doses from CT Imaging

Scanning protocol	**Depth of measurement [cm] (corresponding anatomical structure)**	**Dose [cGy]**
4D	1 (chest wall)	3.5
4D	8 (heart)	2.2
4D	12 (lung)	1.7
3D large chest	1 (chest wall)	3.0

Table 2: Radiation Doses from CBCT and OBI Imaging

Type of imaging	# of imaging sessions	Estimated dose per session	Estimated total dose
CBCT	7	0.61 cGy (x2)	8.54 cGy
CBCT (SBRT)	5	0.61 cGy (x2)	3.05 cGy
OBI	28	0.08 cGy (x4)	8.96 cGy

8.5 SAFEGUARDS IF ANY PARTICIPANTS WILL BE VULNERABLE

Data will be anonymized.

8.6 PRIVACY

Once the patient name and medical record number is removed from the data, there is nothing in that data which could be used to identify patients.

8.7 RISK/BENEFIT

As discussed above, the risk of participating in this study is negligible, except for the inconvenience of spending extra time for additional CT imaging. This study is part of an effort to develop and investigate new methods for inverse radiotherapy plan optimization, which will significantly improve treatment plan quality and therefore reduce volumes and doses to normal tissue to be irradiated. Our studies will benefit future patients receiving radiation therapy for cancer treatment, but the patients enrolled in this study however will not directly benefit from the newly developed approaches. This is not a therapy study. Attending radiation oncologists may use this imaging data to improve the participating subject's therapy, provided that all applicable FDA and IRB guidelines are followed.

9.0 CRITERIA FOR DISCONTINUATION

- Attending physician finds it necessary for patient's health or safety.
- Patient decides to withdraw from the study.
- The sponsor discontinues the study.
- Administrative reasons require patient withdrawal.

Although collecting new information about the subject will be stopped, the study team may still use the information they have already collected to evaluate the study results.

10.0 DATA REPORTING

Data will be submitted according to the protocol requirements for ALL patients registered. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible. A computer based solution will be implemented to maintain a complete record of subject and study information and all processing. Additional files will be used to maintain a record of all subjects grouped within a single project. For the purposes of evaluating the mass-based effects on treatment planning and treatment plan assessment, we will add the following items in the data-management system: (1) Images with outlined treatment volumes for targets and critical structures; (2) Images with outlined for targets and critical structures before, during, and after radiotherapy; (3) TCP, NTCP calculations, dose-volume histograms, dose-mass histograms, gEUDs, and mgEUDs; (4) isdose volumes and isodose masses; (5) Physician reports from follow-up exams.

11.0 INVESTIGATOR'S RESPONSIBILITIES

11.1 Investigator Responsibility/Performance

The investigator will ensure that this study is conducted in accordance with all regulations governing the protection of human subjects.

The investigator will ensure that all work and services described in, or associated with, this protocol will be conducted in accordance with the investigational plan, applicable regulations, and the highest standards of medical and clinical research practice.

11.2 Confidentiality

To safeguard confidentiality, imaging data for patient enrollees will be transferred to a computer workstation which is password-protected and kept in a locked room,

accessible only to institutional personnel. Image data sets will be de-identified by a coding system that assures (a) subsequent image displays contain no patient identifiers and (b) file names are free of patient identifiers. Patient-specific images and other data will be coded using three digit incrementing ID numbers (001, 002, etc.) assigned in order of accrual to the study. The master list documenting association between actual patient name and ID number will be accessible only to the PI. All data will be stored in secure locations on the University of Miami network (i.e., inside the University of Miami firewall).

11.3 Informed Consent and Permission to Use Protected Health Information

It is the responsibility of the investigator(s) to obtain written informed consent from each subject participating in this study after adequate explanation, in lay language, of the methods, objectives, anticipated benefits, and potential hazards of the study. The investigator(s) must also explain that the subject is completely free to refuse to enter the study or to discontinue participation at any time (for any reason). Prior to study enrollment, each subject will sign an IRB approved informed consent form and receive a copy of it (and information leaflet, if appropriate). For subjects not qualified or able to give legal consent, consent must be obtained from a parent, legal guardian, or custodian.

The investigator or designee **must** explain to the subject before enrollment into the study that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and the IRB. It is the investigator's (or designee's) responsibility to obtain permission to use protected health information per HIPAA from each subject, or if appropriate, the subjects' parent or legal guardian.

11.4 Source Documentation and Investigator Files

The investigator must maintain adequate and accurate records to fully document the conduct of the study and to ensure that study data can be subsequently verified.

11.5 Ethics

The investigator agrees to conduct the study in compliance with the protocol, current good clinical practices, and all applicable (local, FDA) regulatory guidelines and standard of ethics.

12.0 REFERENCES

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APPENDIX I:

TABLE 1: STANDARD FRACTIONATION CALENDAR

Assessment	Prior to RT	Between fractions 10 and 20	Follow up visit or atleast 6 weeks post-RT (whichever comes first)
History & Physical Exam	X		X
MRI and/or CT studies (if applicable)	X		X
3D/4D CT scan	X	X	X

TABLE 2: SBRT CALENDAR

Assessment	Prior to RT	Between fraction 3 and fraction 4 of RT	Follow up visit or at least 6 weeks post-RT (whichever comes first)
History & Physical Exam	X		X
MRI and/or CT studies (if applicable)	X		X
3D/4D CT scan	X	X	X