# MRI-only Radiation Therapy Workflow with Continuous Positive Airway Pressure (CPAP) for Motion Management in the Abdomen

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# 1. PROTOCOL SUMMARY AND/OR SCHEMA

- **Specific Objectives**
  - To explore the feasibility of using Magnetic Resonance Imaging (MRI) alone in abdominal radiation therapy for treatment planning and target localization
  - To demonstrate continuous positive airway pressure (CPAP) in motion reduction for abdominal radiation therapy

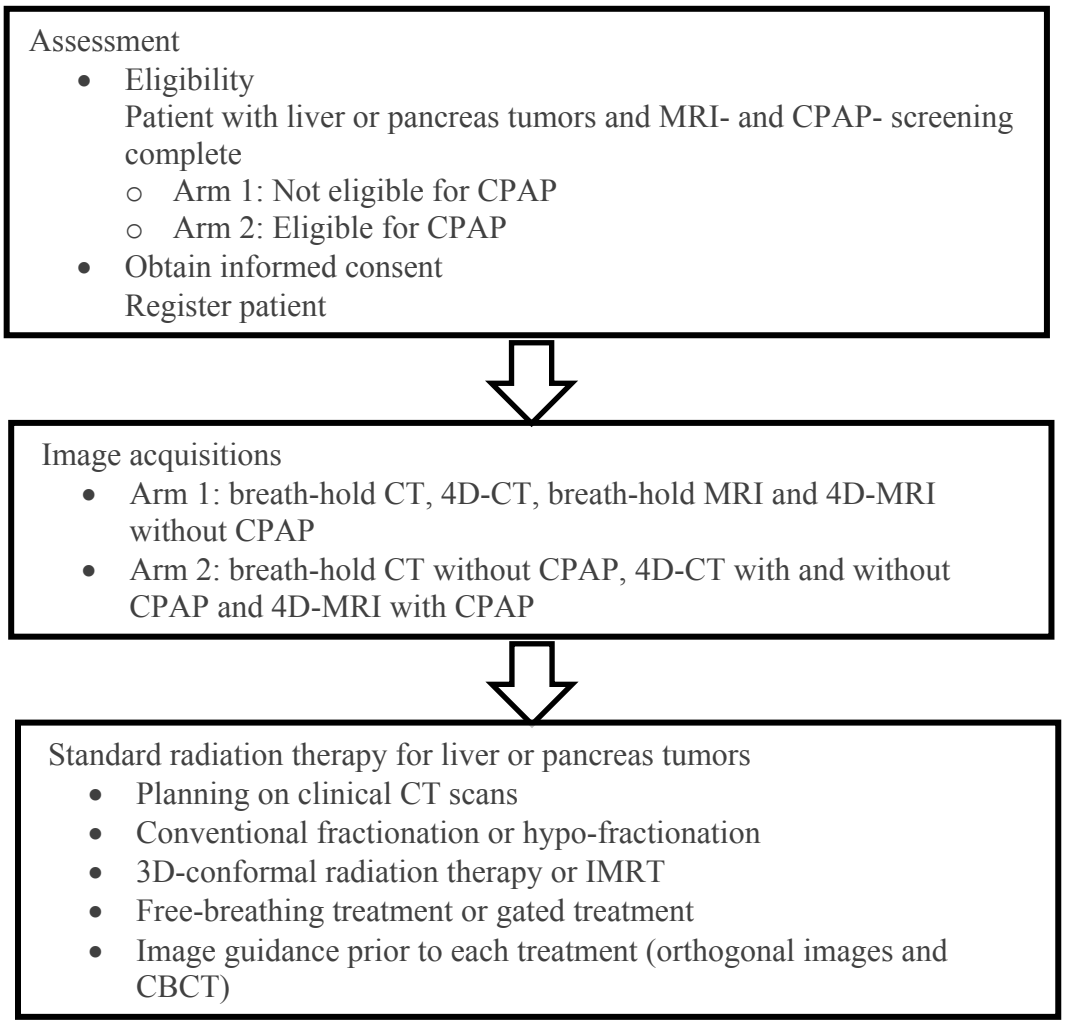
- **Eligibility**
  - Patients who have liver or pancreas tumors and will be treated with radiation therapy

    Patients who are able to commit to Magnetic Resonance Imaging (MRI)

- **Required Sample Size**
  - A maximum of 47 subjects (42 patients + 5 healthy volunteers) over a 24-month period

- **Study Design and Methods**
  - All patients participating in the study will receive standard radiation therapy.
  - Source of data for the study include CT, MRI, cone beam-CT (CBCT) and orthogonal kV/MV images and treatment plans.
  - Patients will undergo both CT and MRI prior to abdominal radiation therapy and CBCT and orthogonal kV/MV images prior to each treatment delivery.
  - A two arm study will be performed and patients will be enrolled into a given arm according to their eligibility. Arm 1 is for patients that are either not eligible for CPAP or that are unable to tolerate CPAP. These patients will undergo breath-hold and 4D imaging for both CT and MRI without CPAP. Arm 2 is for patients that are eligible for CPAP and able to tolerate CPAP. These patients will undergo breath-hold CT without CPAP, 4D-CT with and without CPAP and 4D-MRI with CPAP.
  - Two specific aims will be investigated. In Aim 1, we will explore the feasibility of using a MRI-only in Radiation Oncology workflow. A probabilistic classification method will be utilized to generate a pseudo-CT from MRI to support treatment planning and image guidance for radiation therapy. The quality of the pseudo-CT will be evaluated by comparing it with CT. In addition, the reverse mapping will be investigated to create pseudo-MRI from CBCT to improve visualization of treatment targets and soft tissue prior to treatment delivery. In Aim 2, we will evaluate the utility of CPAP as a novel motion reduction methodology for patients with liver and pancreas cancer, to this end CT images with and without CPAP will be used. The evaluation will be based on the changes of motion magnitude, the achievable volumetric reduction in treatment target volumes, and doses to the targets and critical organs.

- **Schema**




Sample size: a maximum of 42 patients

# 2. INTRODUCTION AND BACKGROUND

## 2.1 Background

Radiation therapy is a technique that delivers high doses to tumors while minimizing doses to neighboring normal tissues in order to achieve optimal treatment outcome. Therefore, this technique requires high accuracy in target localization, one of major issues that are still being investigated in radiation therapy. Accurate targeting is particularly challenging when treating abdominal tumors, such as liver and pancreatic tumors, due to organ motion and the difficulty of distinguishing lesions from neighboring normal tissues using routine Computed Tomography (CT) images that are usually utilized for radiotherapy treatment planning.

In order to clearly identify lesions for radiation therapy, Magnetic Resonance Imaging (MRI) is often used due to its superior soft tissue visualization. MRI also has a potential for measuring biological functions and physiology using various functional imaging modalities, such as dynamic contrast-enhanced and diffusion-weighted images. These advantages allow MRI to be used for more accurate delineation of tumors and critical organs compared to CT and for treatment response assessment. However, MRI is not often used as a sole imaging modality in the radiation therapy workflow since the lack of electron density information precludes heterogeneity corrections, which are part of the standard of care in radiation therapy treatment planning. The use of multi-imaging modalities in the workflow requires an imaging registration step and therefore introduces uncertainties and errors (particularly in contouring) which are then propagated throughout the entire course of radiotherapy. To reduce these uncertainties, it has become of interest to streamline the workflow by implementing MRI alone in the planning process. Investigating the possibility of using MRI alone in the radiation therapy workflow is worthwhile for abdominal radiation therapy. The reason is that MRI is a necessary imaging modality to provide good tissue contrast for contouring abdominal tumors, and the registration uncertainty is likely larger in the abdomen than other body sites due to breathing and gastrointestinal motions.

In regard to organ motion, the largest motion of abdominal tumors and organs is caused by breathing, which complicates the planning process and affects the accuracy of radiation delivery. The American Association of Physics in Medicine (AAPM) Task Group 76 has recommended several methods to manage respiratory motion, and also recommended that respiratory management methods be considered if target motion is greater than 5 mm, or if normal tissue sparing is gained[1]. These methods include motion-encompassing methods, motion reduction methods and real-time tumor tracking methods. Motion-encompassing methods apply a motion margin to the targets to account for respiratory motion, resulting in excess normal tissue being irradiated. Current motion reduction methods use either breath-hold techniques or forced shallow breathing with abdominal compression. Real-time tumor tracking methods involve complicated techniques to detect the motion and dynamically reposition the radiation beam to follow tumor motions. Currently, there are no standard or best motion management options for all patients. However, motion reduction techniques may be simpler ways to address the motion issue while minimizing the injury to normal tissues. Current techniques to reduce the respiratory motion require either patient cooperation for breath-hold or abdominal compression, which may increase discomfort.

### 2.1.1 MRI-only Radiation Therapy Workflow

Several methods have been investigated in order to generate electron density maps from MRI for treatment planning, such as methods that manually identify tissues types and assign bulk densities[2-5], atlas-based methods to automate the process in generating electron density maps[6-9], and voxel-based methods to account for individual differences that are typically lacking in atlas-based methods[10-14]. These studies have shown promising results in terms of pseudo-CT quality, and demonstrated the potential of using MRI alone in the workflow for brain and prostate radiation therapy.

These encouraging results have prompted us to investigate the feasibility of using MRI-only in the abdominal radiotherapy workflow. The goals of using MRI in this workflow include: (1) the delineation of targets and organs-at-risk for treatment planning with enhanced distortion and intensity corrections, (2) the generation of pseudo-CT for dose calculations as well as the generation of digital reconstructed radiographs (DRRs) for image guidance using bony anatomy, and (3) target localization for treatment verification by matching treatment MRI (for MRI on rail) or pseudo-MRI (created from Cone-Beam CT (CBCT) for Linear Accelerator (LINAC) with kilo-voltage (kV) or mega-voltage (MV) on-board imager). To achieve the first goal, geometric distortions, intensity non-uniformity, and motion artifacts will need to be minimized to improve MR imaging quality for contouring and electron density mapping. To address the second goal, we will explore a probabilistic classification method to generate pseudo-CT and DRRs from MRI. This method accounts for individual differences and the mixing of tissue types within voxels that result in the generated pseudo-CT close to true individual anatomy. To address the third goal of using MRI for treatment guidance on the machines equipped with either MRI or kV- (or MV-) CBCT, we will explore the potential of synthesizing pseudo-MRI from CBCT to compensate for the limitation of CBCT in differentiating targets from normal tissues. Our proposed study incorporates MRI into treatment planning and image guidance workflow in order to improve the accuracy and ease of target delineation and localization for abdominal radiation therapy. The result will be not only useful in streamlining the radiation therapy workflow but could also be beneficial for attenuation corrections in PET-MRI.

### 2.1.2 Continuous Positive Airway Pressure (CPAP) for Motion Management

Continuous positive airway pressure (CPAP) has been used in patients with obstructive sleep apnea to maintain airway patency. Other indications include respiratory distress secondary to suspected congestive heart failure, acute cardiogenic pulmonary edema, pneumonia, and chronic obstructive pulmonary disease (asthma, bronchitis, emphysema) [15-17]. This technique provides a constant stream of pressurized air to the upper airways and lungs using a small air pump, tubing, and face/nose mask and may reduce diaphragm motion. An initial study using CPAP for lung radiotherapy indicates that CPAP significantly reduced lung tumor motion compared with free breathing, and therefore reduces treatment volume as well as lung dose. This study has shown the potential of CPAP as a new motion management option in radiotherapy with good reproducibility, simple implementation, and less needs in active patient cooperation [18].

Given these advantages of CPAP, we propose to incorporate CPAP into MRI-only abdominal radiation therapy workflow for motion reduction. The goals of using CPAP in this workflow are: (1) to reduce motion artifacts that degrade the quality of MR images, the quality of the electron density mapping, and the accuracy of target delineation, and (2) to improve targeting accuracy during radiation delivery and thus reduce the injury to neighboring normal tissues.

## 2.2 Hypotheses

Two primary hypotheses are considered in this study: (1) MRI-only abdominal radiation therapy will be a feasible workflow for treatment planning and target localization; (2) the use of CPAP will reduce tumor motion and change internal anatomy in a way that often protects critical organs, and thus allow precise radiation treatment for abdominal lesions while minimizing injury to neighboring normal tissues. We hypothesize that both technologies will be beneficial to patients with abdominal lesions.

## 2.3 Aims

Specific Aim 1: (1) Investigate methods to generate pseudo-CT to support radiotherapy treatment planning and image guidance for abdominal treatments. (2) Explore the feasibility to map CBCT to MRI intensities for improving the visualization of tumors and/or soft tissues for on-line treatment verification using CBCT-based methods. (3) Evaluate the potential role of 4D MRI and their associated pseudo-CT in target delineation for treatment planning and target localization for image guidance.

Specific Aim 2: Determine the effect of CPAP on pseudo-CT image quality, target delineation, tumor motion and dose to critical organs in abdominal radiotherapy.

# 3. INCLUSION/EXCLUSION CRITERIA

## 3.1 Selection of Patient Subjects at the Albert Einstein College of Medicine/Montefiore Medical Center

To study the feasibility of a MRI-only workflow with/or without CPAP in abdominal radiation therapy, the following patients will be **included**:

- Eligibility Criteria
  Patients have liver or pancreas tumors (either primary tumors or metastases) and are scheduled to be treated with radiotherapy (either 3D conformal or intensity-modulation radiotherapy (IMRT) with conventional or hypo- fractionation).
  b. KPS $\geq$ 70
  c. If a biopsy is performed, the patient is at least 1 week post-biopsy.
  d. The patient's age must exceed 18 years.
  e. The patients must be able to commit to T1-weighted, T2-weighted, Dixon fat and water, ultrashort-TE, and other clinical or research MR sequence images prior to treatment.
  f. CPAP Eligibility: CPAP is a safe, effective form of therapy with rare complications. Relative contraindications include patients with bullous lung disease, fibrotic lung disease, Claustrophobia and recurrent sinus or ear infections. The absolute contraindications include obtundation /unconsciousness, chest wall trauma, suspected pneumothorax, persistent nausea/vomiting, active upper GI bleeding, history of recent gastric surgery, facial anomalies/trauma [15,16]. If there is any question about the above history and medical problems, the subject will be referred to a pulmonologist for consultation.
    i. The patients with above contraindications are not CPAP eligible and are enrolled in Arm 1 for the protocol without CPAP
    ii. The eligible patients are enrolled in Arm 2 for the protocol with CPAP.

Exclusion Criteria:
- Patients who meet the following criteria:
  a. Any medical condition, which would make the imaging studies unsafe or poorly tolerated
  b. Known allergic reaction to contrast or shellfish
  c. Implanted metal devices or foreign bodies that serve as a contraindication to MR imaging
  d. Creatinine > 1.4 mg/dl and Creatinine clearance < 20 mg/dl.
  e. Uncontrolled, clinically significant cardiac arrhythmias
  f. Severe claustrophobia
  g. Pregnant female
  h. KPS <70

## 3.2 Selection of Healthy Volunteers at the Albert Einstein College of Medicine/Montefiore Medical Center

To optimize the MRI scanning protocols with and without CPAP volunteers that meet the following eligibility criteria will be **included**:

Eligibilty Criteria
  a. KPS $\geq$ 70
  b. The volunteers' age must exceed 18 years.
  c. The volunteers must be able to undergo T1-weighted, T2-weighted, Dixon fat and water, ultrashort-TE, and other clinical or research MR sequence images prior to treatment.

d. CPAP Eligibility: CPAP is a safe, effective form of therapy with rare complications. Relative contraindications include volunteers with bullous lung disease, fibrotic lung disease, Claustrophobia and recurrent sinus or ear infections. The absolute contraindications include obtundation /unconsciousness, chest wall trauma, suspected pneumothorax, persistent nausea/vomiting, active upper GI bleeding, history of recent gastric surgery, facial anomalies/trauma [15,16]. If there is any question about the above history and medical problems, the volunteer will be not be included in the pilot study.

Exclusion Criteria:

- Volunteers who meet the following criteria:
  a. Any medical condition, which would make the imaging studies unsafe or poorly tolerated
  b. Implanted metal devices or foreign bodies that serve as a contraindication to MR imaging
  c. Uncontrolled, clinically significant cardiac arrhythmias
  d. Severe claustrophobia
     Pregnant female
  f. KPS <70

# 4. STUDY DESIGN AND METHODS

## 4.1 Recruitment of Subjects

Patients having either liver or pancreas cancer, who will be treated with radiation therapy will be invited to participate in the study during patient consult.

We will enroll up to five volunteers in the preliminary study to optimize the MR scanning protocols to be used in the patient study. We will place flyers to recruit healthy volunteers from Montefiore Medical Center or Albert Einstein College of Medicine. All eligible volunteers that can undergo CPAP and MRI scanning will be accepted into the volunteer study. No remuneration to volunteers will be offered and there are no potential benefits other than the Radiology read of the MRI for incidental findings. There are no risks to volunteers participating in the study related to radiation exposure because only MRI will be performed.

## 4.2 Registration Procedures

- Patients who agree to participate in the study and who provide written informed consent will be enrolled.
- Patients must meet all eligibility criteria listed in Section 3. The study coordinator will verify eligibility, assign a case number, and register the patient prior to study specific participation. The following information will be recorded:
  - Protocol number
  - Patient's initials
  - Patient's medical record number
  - Patient demographic data, including gender, birth date, and race.

## 4.3 Study Design

### 4.3.1 A Volunteer Study to Optimize MRI Scanning Protocols with and without CPAP

Prior to enrolling patients in the study, a volunteer study will be conducted to optimize MRI scanning protocols with and without CPAP. The purpose of the volunteer study is to gain experience in using CPAP, to investigate appropriate MR imaging protocols with sufficient image resolution and contrast, and to test and streamline the workflow to minimize possible patient discomfort. Volunteers will not receive any MR contrast as part of their MR imaging and will be imaged two times once without the use of CPAP and once using CPAP employing the following

MR sequences: T1-weighted, T2-weighted, Dixon fat/water, ultra-short TE and other clinical or research MR sequences.

### 4.3.2 Image Acquisitions: CT, MRI, CBCT and orthogonal kV/MV images

We are planning to enroll a maximum of 42 patients into this study. Prior to abdominal radiotherapy, all eligible participants will undergo both CT and MRI scans in the radiotherapy treatment position. Two scanning protocols (Arm 1 and Arm 2) will be performed according to their CPAP eligibility.

(1) Arm 1: For patients not eligible for CPAP or unable to tolerate CPAP
- Breath-hold CT and 4D-CT without CPAP
- Breath-hold MRI and 4D-MRI without CPAP
  - T1-weighted, T2-weighted, Dixon fat/water, and ultra-short TE images

(2) Arm 2: For patients eligible for CPAP and able to tolerate CPAP
- Breath-hold CT without CPAP
- 4D-CT with and without CPAP
- 4D-MRI with CPAP
  - T1-weighted, T2-weighted, Dixon fat/water, and ultra-short TE images

CT scans will be performed in the axial scanning mode with ~2 mm slice thickness over the entire abdomen region for treatment planning and dose calculations.

MRI images using standard clinical imaging sequences will be acquired, including T1-weighted, T2-weighted, and Dixon fat and water images. Additional MRI scans, such as ultrashort-TE (UTE) images, will follow MRI safety guideline of FDA and will be optimized based on phantom and volunteer studies before clinical studies. Gadolinium-based contrast may be administered per institutional routine and research protocol. The MRI scanning sequences for these MRI images will be optimized to achieve optimal resolution (~ 2 mm) and contrast with minimized geometric distortion (< 2 mm). MR images will be used (1) to delineate the targets following the standard treatment planning process, and (2) to create pseudo-CT for dose calculations and to be compared with CT-based dose calculations.

Patients will receive standard radiotherapy to liver or pancreatic lesions using 3D-conformal or IMRT techniques (using CT-based planning without CPAP motion management). Prior to each treatment delivery, patients will undergo kV/MV orthogonal images and CBCT scans, and the CBCT scans will be compared with the planned CT to verify treatment position. In off-line, the CBCT scans and kV/MV orthogonal images will be compared with pseudo-CT and DRRs that are created from pseudo-CT.

### 4.3.3 CPAP Procedures for Eligible Patients Enrolled in Arm 2

Before simulation and image acquisition with CPAP, patients will be fitted with a mask by a respiratory therapist and then undergo training on use of the CPAP device. Under physician supervision, patients will be instructed how to gradually increase air pressure from 5 cm $H_2O$ to the maximal comfortably tolerated level up to a maximum of 15 cm $H_2O$. Patients were connected to CPAP for at least half an hour before undergoing image acquisition.

If CT and MRI scans could not be performed at the same day, patients will be discharged home with their mask, hose, and filter and be asked to bring them for next image acquisition. Detailed procedures are described as below,

(1) Place patient in a sitting position
(2) Assess vital signs every 15 minutes in the first hour and then every half an hour while on CPAP and monitor SpO2 continuously

(3) If systolic BP <90 mmHg contact Medical Control prior to beginning CPAP to assess patient stability
(4) Begin at lowest level of positive pressure available
(5) Explain the procedure to the patient:
(6) Patient requires reassurance to be used effectively.
    a. Example: “You are going to feel some pressure from the mask”
(7) Place delivery device over mouth and/or nose. (depend on the type of mask is used) Instruct patient to breath in through their nose slowly and exhale through their mouth as long as possible (count slowly and aloud to four then instruct to inhale slowly).
(8) Check for air leaks
(9) Documentation on the patient care record should include:
    a. CPAP level
    b. Frequent SpO2 and Vital Sign assessment
    c. Any adverse reactions

### 4.3.4 Methodology Development to Create Pseudo-CT from MRI and Its Evaluation

A method of using probabilistic classification of MRI to generate pseudo-CT has shown promising results in brain radiation therapy [11,19]. The probabilistic classification accounts for individual differences and the mixing of tissue types within voxel that result in the generated pseudo-CT close to true individual anatomy. We will first explore the potential of using this classification method to generate pseudo-CT in the abdomen, and then may explore a hybrid method (a combination of atlas- and voxel- based methods) to improve the quality of pseudo-CT. Probabilistic tissue classification is achieved via fuzzy c-means (FCM) clustering with a spatial constraint [11]. The FCM algorithm assigns voxels of the images a probability of belonging to a class. Membership probability in any given tissue class varies between zero and one. The membership for each voxel can be obtained by minimizing the objective function. Then relative attenuation properties are assigned based on the probability map and pseudo-CT is generated.

To evaluate the quality of pseudo-CT in treatment planning, 3D-conformal and IMRT plans will be created on standard CT and then the plans will be mapped onto pseudo-CT. Dose distributions and dose volume histograms will be compared between the plans using CT and pseudo-CT datasets.

To evaluate the quality of pseudo-CT in image guidance using bony structure, DRRs generated from pseudo-CT and CT will be both aligned to the orthogonal images that are taken prior to treatment. To evaluate the quality of pseudo-CT in image guidance using soft tissue, pseudo-CT and CT will be both aligned to CBCT that are taken prior to treatment. The accuracy of image alignment using pseudo-CT will be evaluated.

### 4.3.5 Methodology Development to Create Pseudo-MRI from CBCT and Its Evaluation

CBCT has a limitation in differentiating targets from normal tissues. To better visualize targets and soft tissues, the method to synthesize MRI will be explored. The proposed method will use planning MRI images and their associated pseudo-CT images as well as CBCT images. First, CBCT is registered to pseudo-CT using rigid or deformable registration. Second, the transformation information from the previous registration is applied to the planning MRI to generate a synthetic CBCT-based MRI for target localization and alignment during treatment. To evaluate the quality of pseudo-MRI in target localization and alignment, the alignment using pseudo-MRI and planning CT will be compared with the alignment using CBCT and planning CT.

### 4.3.6 Study of the Potential Role of 4D-MRI in Treatment Planning and Image Guidance

4D-CT is usually acquired for motion assessment and management when treating tumors in chest and abdomen. When contouring target volumes, internal target volume (ITV) is defined based on the 4D-CT dataset in order to account for target motion. For abdominal tumors, it is challenging to directly assess target motion on 4D-CT without contrast administration or implantation of fiducial

markers. Thus, replacement of 4D-CT with 4D-MRI would be a beneficial step for motion assessment and an important part in the MRI-alone workflow for abdominal radiotherapy. To investigate the role of 4D-MRI in treatment planning, ITVs contoured using 4D-CT and 4D-MRI will be compared, and their dosimetric impact will be also evaluated.

#### 4.3.7 CPAP Effect on Motion Reduction and Clinical Treatment Outcome

CT images will be acquired without and with CPAP for patients enrolled in Arm 2. Following routine contouring and planning procedures for abdominal treatment, gross tumor volume (GTV) and clinical target volume (CTV), ITV to account for tumor motion, and planning target volume (PTV) to account for setup errors will be identified and contoured on each CT dataset. Treatment plans will be generated on both CT datasets with their corresponding target contours using the same plan objectives.

To evaluate motion reduction using CPAP, tumor excursion (in superior-inferior, right-left and anterior-posterior directions) and ITV will be calculated and compared between two datasets for Arm 2 participants. To evaluate the change on clinical outcome, dose metrics such as mean dose to critical organs and complication rates will be compared.

### 4.4 Clinical MRI Assessment

All images will be reviewed by a board certified radiologist to assess for unexpected findings. In case of unexpected clinically relevant imaging findings the Study-PI, Dr. Madhur Garg, will inform study participants of these findings.

## 5 STATISTICAL CONSIDERATIONS

### 5.1 Statistical Considerations for Specific Aim 1

The primary clinical end point of specific aim 1 is to show the non-inferiority of the 4D-MR only workflow for ITV definition to that using 4D-CT. In the case of lung cancer Ehler et al. [20] have found using 4D-CT that different methodologies for the definition of the ITV yielded differences in ITV definition ranging from 1.7% to 43% with an average difference between methodologies of 17.5% . The observed differences in volume definition where confined to the periphery of the ITV volume. Therefore a difference of no larger than 14% between the ITV defined using our proposed 4D MR workflow versus 4D CT is considered as not being clinically meaningful. Based on the literature assuming a standard deviation of 16.3% and a non-inferiority margin of 14% in ITV volume definition between 4D-MR and 4D-CT, we find that if there is truly no difference between the ITV definition using 4D-CT and the ITV definition using 4D-MR. A sample size of 21 patients will achieve a 91% power to detect the non-inferiority using a one sided t-test and the true difference between the mean is 0.at a type 1 error rate of 0.01.

### 5.2 Statistical Considerations for Specific Aim 2

Using a conventional motion reduction technique employing an abdominal compression pillow we have found an average motion reduction of 12% with a standard deviation of 13% for lesions within the lung [21]. Achievable motion reduction ranged from 3% to 28%, therefore an average motion reduction of at least 12% with CPAP is considered clinically meaningful. Using pairwise analysis assuming a mean difference of 12% between free breathing and the application of CPAP with an associated standard deviation of 13%, and an $\alpha$=0.01, using a two sided paired t-test we find that with 21 patients will have 90% power to detect a motion reduction of at least 12% when using CPAP. Assuming an allocation ratio of 1:1 between the two arms of this study we are planning to recruit a maximum of 42 patients to this study, however once, 21 patients have been

accrued to the CPAP arm no further patients will be enrolled into that part of the study and the study will be closed once the necessary patient number for aim 1 has been achieved.

# 6 EXPECTED ADVERSE EVENTS

## 6.1 MRI Scans

MRI Scan:
Anxiety/Stress
Claustrophobia
Discomfort

Gadolinium:
Allergic reaction to contrast agent
Headache
Nausea
Vomiting
Rash
Temporary low blood pressure
Nephrogenic Systemic Fibrosis (NSF)/Nephrogenic Fibrosing Dermopathy (NFD).

NOTE: Precautions should be exercised for patients with a history of grand mal seizures, severely impaired renal function or hemolytic anemia. The very unlikely possibility of a reaction, including anaphylactic or cardiovascular reactions, should be considered especially for patients with a known sensitivity to Gadolinium or history of asthma. Nephrogenic Systemic Fibrosis (NSF) or Nephrogenic Fibrosing Dermopathy (NFD) (kidney disorders), may occur in patients with moderate to end-stage kidney disease after they have had a MRI scan with gadolinium-based contrast agent.

Needle Placement**:**
Minor discomfort;
Bleeding;
Infection;
Bruising.

## 6.2 CPAP

CPAP is a safe form of therapy with relatively few recorded major complications. Hypotension, local skin irritation, drying of the nasal and pharyngeal membranes, nasal congestion/rhinorrhea, gastric distention, vomiting, and eye irritation are the rare adverse events. Nevertheless, minor discomfort and complaints regarding the mask interface remain relatively common[15].

# 7 PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK

## 7.1 Human Subjects Involvement and Characteristics

We expect to enroll a maximum of 47 subjects (42 patients + 5 healthy volunteer subjects) over a 24-month period. For each patient participating in the study, the research will involve a pretreatment MRI and CT scans and treatment CBCT and orthogonal kV/MV images as described in Section 3. No patients will be excluded based on racial/ethnic or sex/gender.

## 7.2 Source of Materials

The source of data consists of CT, MRI, CBCT and orthogonal kV/MV images and treatment plans as described in Section 3. A data record will be kept in a locked cabinet in the project leader's office, which will be accessible only to the scientific staff involved with this research project.

## 7.3 Potential Risks and Protection against Risks

The MRI scans are minimally invasive. The only contraindications to a MRI scan are the presence of any ferrous metal in the body or claustrophobia. Prior to arriving at the MRI facility, all patients will be required to complete a standard clinical screening form for any metallic implants or ferrous material they may have in their bodies. Any presence of such material will immediately disqualify them from the study.

CPAP is a safe form of therapy with rare complications. Relative contraindications include patients with bullous lung disease, fibrotic lung disease, Claustrophobia and recurrent sinus or ear infections. The absolute contraindications include obtundation /unconsciousness, chest wall trauma, suspected pneumothorax, persistent nausea/vomiting, active upper GI bleeding, history of recent gastric surgery, facial anomalies/trauma. All patients will be required to complete a screening form for any of these histories. Any presence of these histories will immediately disqualify them from Arm 2 protocol. If there is any question about the above history and medical problems, the patient will be referred to a pulmonologist for consultation.

## 7.4 Recruitment and Informed Consent

Drs. Garg, Bodner, Kabarriti, and Ohri will recruit patients for this study, and Dr. Sadoughi will evaluate if patients are eligible to be enrolled in Arm 2 CPAP protocol. The patients who participate in the study will be screened, educated, and consented. Most imaging protocols described in this research proposal are routine clinical imaging protocols in use at our institution. Imaging sequences that usually are not used in abdominal scans will be optimized and tested on volunteers before using them in patients who participate in the study (Refer to Section 4.3.3).

# 8 DATA AND SAFETY MONITORING PLAN

Adverse events will be collected and reported according to a DSMP described in Appendix I.

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# APPENDIX I

## OVERSIGHT AND MONITORING PLAN

The Albert Einstein College of Medicine/Albert Einstein Cancer Center Data Safety Monitoring Committee (DSMC) has the responsibility for ensuring data and safety monitoring along with the PI who is ultimately responsible for the ongoing monitoring and safety of clinical protocols. The primary functions of the AECC DSMC are as follows:

1. To review and ensure protocol compliance with dose escalation in phase I trials
2. To review/assure protocol compliance for all trials that have two-stage phase II designs,
3. Reviewing all internal and external serious adverse reports, investigator alerts, action letters, and other safety reports for trials being performed at AECC-affiliated institutions and;
   To implement and to determine the adequacy of DSM plans of all approved protocols.

The DSMC is an independent committee and meets on a monthly basis. During its monthly meeting, the DSMC will review serious adverse events from this study. In the event that the DSMC decides that a revision is warranted, the committee will immediately notify the principal investigator of this study. The DSMC has the authority to close trials to patient accrual should the risk to patients be excessive or outweigh the potential benefits of the study. All study suspensions and closures will be forwarded to the IRB/CCI and study sponsor from the DSMC.

## MONITORING AND REPORTING GUIDELINES

An adverse event can occur on any clinical trial; it is the responsibility of the PI and the research team to identify, review, and report all necessary adverse events to the institutional IRB, the sponsor, and governmental agencies (i.e., NCI and/or FDA) as appropriate. Adverse events should be identified through standard, routine protocol review and clinical assessment of each subject participating in the clinical trial. This review should be timely in order to meet the requirements for adverse event reporting defined below:

Adverse Event (AE)
An adverse event is defined by the GCP (Good Clinical Practice guidelines) as an undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational products.

Serious Adverse Event (SAE)
A serious adverse event is an adverse experience that fits one or more of the conditions noted below:

1. Fatal or life threatening
2. Disabling
3. Results in hospitalization or prolongation of hospitalization
4. Results in a congenital anomaly or occurrence of malignancy

All Serious Adverse Events, regardless if they are unrelated to study treatment, should be reported to the IRB and sponsors. These include, but may not be limited to:

1. All deaths
2. All SAE associated with study procedures
3. Any serious problem
4. Any recurring problem
5. Any outside AE report
6. Any unanticipated side effects

Unexpected Adverse Event
An unexpected AE is an experience not previously reported (in nature, severity, or incidence) in the current Investigator's Brochure or protocol document.

**EXPEDITED REPORTING OF ADVERSE EVENTS**

Depending on the nature, severity, and attribution of the event an ADR report will be phoned in, submitted in writing, or both according to the table below. Telephoned Adverse Events must also be reported by email to the AECC DSMC within one working day of the event. All adverse events must also be reported to the Montefiore Medical Center IRB, and any sponsor/funding agency not already included in the list.

**Telephone reports to:**
Study Co-Chair: Madhur Garg, MD
Phone: 718-920-4140
Fax: 718-531-2064

**Written reports to:**
Kathy O'Connor, MMC IRB
Fax: (718) 515-5217

MMC IRB – Copy of final written report to Sponsor.

**EXPEDITED REPORTING TABLE**

| **Summary of Reporting Requirements for Adverse Events** | |
|---|---|
| **Expedited Reporting** | |
| **Unexpected Events** | |
| **GRADES 2 and 3**<br>Attribution of possible, probably or definite | **GRADES 4 and 5**<br>Regardless of attribution |
| Expedited report within 15 working days to FDA<br><br>(Grade 1 – Adverse Event Expedited Reporting NOT required) | Report by phone to FDA within 24 hours. Expedited report to follow within 15 working days.<br><br>This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution.<br><br>Any late death attributed to the agent (possible, probable, or definite) should be reported within 15 working days. |

**For Hospitalization Only** – Any medical event equivalent to the CTC Grade 3, 4, 5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for phase of study, expected or unexpected and attribution.

Expedited reporting may not be appropriate for specific expected events for certain later phase 2 and phase 3 protocols. In those situations the adverse events that will not have expedited reporting must be specified in the text of the approved protocol. An expected grade 3 event that is using the generic reporting criteria, for instance. In a trial of investigational agents where grade 3 diarrhea requiring hospitalization is expected, only diarrhea requiring ICU care (grade 4) might be designated for expedited reporting.