Protocol Title: Longitudinal MR Imaging of Pulmonary Function in Patients Receiving Thoracic Radiation Treatment

NCT02478255

Protocol Version Date: 26Jul2018

DUKE CANCER INSTITUTE

A National Cancer Institute-designated Comprehensive Cancer Center

Longitudinal MR Imaging of Pulmonary Function in Patients Receiving Thoracic Radiation Treatment

Sponsor:	PI – Duke Cancer Institute
Funding Source:	NIH
Protocol Source:	PI - Duke Cancer Institute
Duke IRB#:	Pro00059856

Principal Investigator

Joseph Mammarappallil, MD PhD

(919) 684-2051

joseph.mammarappallil@duke.edu

Co-Principal Investigator(s)

(Main Contact)

Bastiaan Driehuys, PhD

bastiaan.driehuys@dm.duke.edu

(919)684-7786

Sub-Investigator(s)

Christopher Kelsey, MD

kelse003@mc.duke.edu

Statistician

Xiaofei Wang

xiaofei.wang@duke.edu

Lead Study Coordinator and Regulatory Coordinator

Samantha Womack

sam.womack@duke.edu

Data Manager

Bastiaan Driehuys, PhD

Original version:	Date
Amended version	Date 26Jul2018

1. Protocol Title: Longitudinal MR Imaging of Pulmonary Function in Patients Receiving Thoracic Radiation Treatment Pro00059856

2. Purpose of the Study: The purpose of this study is to evaluate a comprehensive MRI-based protocol designed to image alterations in regional lung function that occur when patients receive thoracic radiation therapy. Radiation therapy (RT), when applied to tumors in or around the thorax, is known to cause regional lung injury (as defined by imaging changes reflecting reduced perfusion, reduced ventilation, and increased density) typically evolving 1-6 months post-RT. Approximately 5-20% of patients experience global lung dysfunction manifested as dyspnea after RT. This often occurs before imaging abnormalities are detected by conventional modalities (CT, SPECT). The exact linkage between the changes in imaging and the development of symptoms is unclear (for example, the time course of the two do not match exactly).

Presently, there are no well-accepted methods to predict a given patient's risk of developing dyspnea after RT, and none of the prior studies have addressed regional gas exchange (which might be considered the inherent function of the lung). Thus, there exists a considerable need to develop new methods to accurately detect and monitor radiation-induced injury, especially in the early post-RT time period when most patients develop clinical symptoms.

The protocol will leverage advances in MRI imaging that facilitate the assessment gas exchange, as well as pulmonary structure, ventilation, and perfusion within a single integrated MRI exam. Pulmonary ventilation and gas exchange are assessed 3-dimensionally by using inhaled hyperpolarized ^{129}Xe MRI, which has been developed at Duke over the past 4 years under IRB protocol Pro00025110 and IND #109,490. In addition to this, pulse sequences have been implemented that complement this information with 3D isotropic ^{1}H MR imaging of pulmonary structure and pulmonary perfusion. Perfusion is imaged following i.v. injection of an approved macrocyclic MRI contrast agent. Hence, the technology is now available at Duke, for a fully 3D MRI protocol capable of assessing all relevant aspects of pulmonary structure and function in a single exam. Since this approach does not use ionizing radiation, it can more safely be utilized to follow patients over time.

Our aim is to now apply this set of imaging tests to objectively assert RT-associated changes in regional lung function. Patients undergoing radiation therapy will be scanned at baseline prior to RT, and serially post-RT over a temporal window ranging out to 6 months post- RT. The exact timing of these post-RT assessments will be altered based on our initial results. The primary study objective is to evaluate dose- and time–dependence of RT-induced changes in MRI-defined local function/structure. Our primary hypothesis is that pulmonary function measured by MRI will worsen after radiation therapy compared to baseline. The secondary study objective will test whether particular imaging features at baseline can predict the degree of radiation-induced lung injury that will develop. We will compare the sensitivity with which MRI can detect changing pulmonary status to that of conventional pulmonary function testing.

3. Background and Significance: Radiation therapy when applied to tumors in or around the thorax is known to cause regional lung injury. Approximately 5-20% of patients experience dyspnea after RT and a larger fraction exhibits subclinical reductions in pulmonary function. Unfortunately, there are no well-accepted methods to predict a given patient's risk of developing dyspnea after RT. Potential risk has been proposed to be predictable by patient-specific factors (age, smoking history, tumor location, gender) and treatment-specific factors (chemotherapy regimen and dose). However none of these have been consistently demonstrated across different studies. Moreover, controversy persists about which radiation dose parameters optimally predict the risk of radiation pneumonitis (lung volume or total dose). Furthermore, several medications have been evaluated for their ability to reduce radiation pneumonitis, but results have been mixed. A fundamental impediment to addressing all of these questions is that the pulmonary toxicity of irradiation does not significantly alter most standard pulmonary function tests. This is further compounded by the fact that radiation-induced injury is focal, whereas PFTs can only assess the lung as a whole.

The shortcomings of global pulmonary function tests have led to increasing interest in using 3-dimensional functional imaging to evaluate radiation-induced lung injury (RILI). Marks and others have conducted seminal studies of single-photon computed tomography (SPECT) to assess perfusion changes longitudinally in RT patients. However, SPECT imaging requires injection of radioactive 99mTc contrast agent, and suffers from relatively poor spatial and temporal resolution. Moreover, SPECT can currently only image pulmonary perfusion and not pulmonary structure, ventilation or gas-exchange. Instead, MRI now presents the opportunity to deploy a much more comprehensive and non-invasive approach to imaging pulmonary structure and function in a single exam. This capability should provide fundamental new insights regarding the origins of radiation-induced lung injury (RILI) and lay the groundwork to find ways to both predict it and treat it.

Over the past 4 years of development, hyperpolarized ^{129}Xe MRI has demonstrated the ability visualize pulmonary ventilation with high resolution. Moreover, by exploiting the moderate solubility of ^{129}Xe in blood and pulmonary tissues, combined with its unique frequency shifts, it is now feasible to image the transfer of this gas from airspaces into the pulmonary capillary blood. Such 3-dimensional imaging of gas exchange has not been previously possible by any technique and provides a fundamentally new window on regional pulmonary gas exchange. The technique has been shown to be safe and well tolerated in human subjects. This was demonstrated by a phase I clinical trial for HP ^{129}Xe MRI that was completed at Duke and published in the journal Radiology in 2012. This study enrolled 44 patients and healthy volunteers and demonstrated that inhalation of up to four 1 liter doses of HP ^{129}Xe was well-tolerated, generated no notable changes in measured physiologic parameters and resulted in no SAEs or withdrawals. The study involved developing a substantial technical infrastructure (polarizers, coils, phantoms, scanner upgrades) that is now available and used for clinical research at Duke. Since the completion of that study 100 additional patients and volunteers have been scanned, each of whom have inhaled with multiple doses of ^{129}Xe without incident.

While ventilation and gas exchange as assessed by hyperpolarized ^{129}Xe MRI provide a useful view on pulmonary function, there is additional value in adding structural and functional information provided by conventional ^{1}H MRI. Lung structure can now be imaged using an ultrashort-echo time (UTE) sequence during a 4 min free-breathing scan. Such a scan will reveal local tissue density, edema, and other anatomical landmarks. Moreover, with the addition of a single injection of MR contrast agent, a 3D isotropic image of pulmonary perfusion can also be obtained. Thus, by combining HP ^{129}Xe and ^{1}H MRI, we can comprehensively assess both the structure and function of the irradiated lung longitudinally.

4. Design and Procedures: This will be an unblinded, open-label study enrolling patients who are scheduled to undergo thoracic radiation therapy as part of their standard clinical care as well as healthy volunteers. Approximately 35 subjects will be consented including screen fails. Subjects to be enrolled will include males and females over 18 years old, for a targeted enrollment of 20 subjects undergoing RT. An additional 10 healthy volunteers will be enrolled to optimize the MRI parameters and provide reference images for normal pulmonary function. After consent and screening, healthy volunteers will undergo just one study visit. Patients scheduled for RT will be seen up to 2 time points after consent and screening with an optional 3rd time point– a baseline Visit 1 (before RT begins), Visit 2 (at ten-fourteen weeks post RT) and optional visit 3 (thiry-two to forty weeks post RT). For patients who participate in 2 visits, their participation will last until approximately 4 months after RT is completed, while patients completing the optional 3rd visit will participate until 12 months after RT. At each visit, subjects will undergo pulmonary function testing and MRI. The objective of the MRI session is to acquire 3D images of pulmonary structure, ventilation, gas exchange and perfusion. Each session should take approximately 3 hours of the subject's time.

The study begins with detailed pulmonary function testing and the collection of relevant patient history and symptoms. Pulmonary function testing will include one or more of spirometry, lung volumes, DL_{CO} and impulse oscillometry. The subject will be escorted to the MRI suite where they will be fitted with a ^{129}Xe transmit-receive vest coil. They will then be positioned supine on the scanner bed. They will be coached about how to inhale hyperpolarized ^{129}Xe from the dose delivery bags. Then the subject and bed will be moved into the scanner and they will undergo basic ^{1}H localizer and anatomical scans. Once localization is complete, subjects will undergo several MRI scans after inhalation of HP ^{129}Xe. Each dose will be limited to a volume less than 25% of subject lung capacity (TLC) as is the case for our ongoing protocol Pro00025110. After each ^{129}Xe dose, the table will be moved out of the magnet bore and the subject queried for any symptoms. The next ^{129}Xe dose and scan will be administered when the subject and study personnel are ready. Subjects will undergo a calibration ^{129}Xe MR spectroscopy scan, ^{129}Xe ventilation MRI, and ^{129}Xe gas exchange MRI. A given ^{129}Xe MRI scan may be repeated, if necessary. There is no limit to the number of ^{129}Xe scans allowed during the session although current ^{129}Xe production capabilities are only sufficient to generate 5 ^{129}Xe doses per imaging session. After completing the ^{129}Xe portion of the scan, the ^{129}Xe coil will be removed and

patients fitted with a torso array ^{1}H coil. They will then undergo a free-breathing ultra-short-echo time ^{1}H MRI to delineate lung structure.. This completes the MRI exam, after which subjects will be free to go home or continue with their standard clinical care. All subjects will be evaluated at one center, Duke University, in Durham, NC, USA.

5. Selection of Subjects: In addition to healthy volunteers, the population to be studied will consist of patients scheduled to undergo RT for either lung cancer or other malignancies such as breast cancer or lymphoma that involve significant irradiation of the thoracic cavity. Before each MRI session, the following criteria will be assessed in order to minimize risk to the subjects.

Inclusion Criteria

1. Patient scheduled to undergo thoracic RT at Duke University to a dose of at least 20 Gy
2. Willing and able to give informed consent and adhere to visit/protocol schedules

Exclusion Criteria:

1. Subject is less than 18 years old
2. MRI is contraindicated based on responses to MRI Screening questionnaire
3. Subject is pregnant or lactating
4. Respiratory illness of a bacterial or viral etiology within 30 days of MRI
5. Subject has any form of known cardiac arrhythmia
6. Subject does not fit into ^{129}Xe vest coil used for MRI
7. Subject cannot hold his/her breath for 15 seconds
8. Subject deemed unlikely to be able to comply with instructions during imaging
9. Medical or psychological conditions which, in the opinion of the investigator, might create undue risk to the subject or interfere with the subject's ability to comply with the protocol requirements.

Inclusion/Exclusion Criteria for Healthy Volunteers

1. Subject meets all criteria above but does not have a clinical diagnosis of respiratory disease.

Subject Identification: Upon providing consent, the subject will be assigned a subject identification number (SIN), which will be used for all data collection and imaging studies. The SIN will consist of a study identifier and four digit extension (e.g. -0001 for the first subject).

6. Subject Recruitment and Compensation: Healthy volunteers as well as patients who will be undergoing thoracic radiation therapy will be recruited via flyers and website postings. Patients scheduled to undergo thoracic radiation at Duke University may also be informed about study participation by their physician or physician's staff. If they are interested in participating and appear to meet all inclusion criteria they will be referred to the study coordinator for formal consenting. It is expected that up to 10 healthy volunteers and 25 patients scheduled for RT will

be recruited in this first phase of the study. Recruitment will be open to all demographic groups. Subjects will be compensated after each study visit for their travel/parking and time. If a procedure has to be cancelled for technical reasons after a subject has arrived on site, the subject will be compensated as though he/she had completed the study. The subject will be encouraged, but not required to return at a later date to complete the procedure. If the subject returns, he/she will be compensated again.

7. Consent Process: The study coordinator will consent prospective participants. If necessary, the participants will have no less than 24 hours to consider their participation. Consenting will take place in a private room. The prospective participant may have family or a friend present during the consent process if they wish. At least an hour will be slotted for the consent process but we will not prevent the subject from asking questions beyond that time. If the subject wishes to consider the study overnight or longer, an additional appointment will be made for the subject to continue the consent process. From the time of initial contact until the participant completes the study they will have complete freedom to access the coordinator by phone, email, or in person.

8. Subject's Capacity to Give Legally Effective Consent: Subjects without capacity to give consent will not be recruited in this study.

9. Study Interventions: Hyperpolarized xenon will be administered in multiple doses in volumes up to 25% of subject TLC followed by a breath hold of up to 15 seconds. Subsequent ^{129}Xe doses will only be administered once the subject is ready to proceed. Hyperpolarized ^{129}Xe MRI will be used to acquire one or all of the following data:

1. ^{129}Xe calibration dose to test coil tuning and loading in each subject to permit optimal setting of imaging parameters.
2. ^{129}Xe distribution after inhalation and breath-hold as an indicator of regional pulmonary ventilation.
3. ^{129}Xe signal dissolved in the pulmonary interstitial spaces and capillary blood as an indicator of pulmonary gas exchange.
4. ^{129}Xe spectroscopy to follow the dynamics of gaseous and dissolved-phase ^{129}Xe.

Conventional ^{1}H MRI will be used to provide anatomical reference scans, as well as pulmonary perfusion. These will include some or all of the following:

1. 3-Plane Localizer
2. Breath-hold steady-state-free-precession image to highlight the vasculature.
3. Breath-hold 3D radial MRI to delineate the thoracic cavity
4. Free-breathing UTE 1H MRI to image tissue density and edema

10. Risk/Benefit Assessment: As this is the first comprehensive study of its kind in patients undergoing RT, it is not known if the data generated will be of direct benefit to the patients. It is certainly possible that images obtained from these studies will assist in the clinical management of the patients. For example, the pre-radiation scans may provide information regarding the

distribution of function within the lung that may aid in the design of radiation therapy portals. The post-radiation images may help in better understanding the causes of pulmonary symptoms that the patients may develop. For healthy volunteers, there will be no direct benefit. However, the knowledge gained from these studies is expected to benefit future patients who may undergo thoracic RT.

Risks of Hyperpolarized ^{129}Xe Inhalation of hyperpolarized ^{129}Xe may carry some minor risks. Xenon is a general anesthetic when breathed continuously at concentrations greater than 70% for extended periods of time. In the proposed study, xenon will be delivered in a single breath, with alveolar concentrations below 25%. At these concentrations, subjects may experience transient effects including dizziness, slight tingling or numbness of the extremities, nausea, smelling of flowers, or a feeling of well-being and euphoria. These effects will wane within 1-2 minutes of exhaling the xenon and are documented in the consent forms.

A second risk comes from administering HP ^{129}Xe without oxygen. This is necessary to preserve good image quality, because O_2 is paramagnetic and depolarizes the HP ^{129}Xe. Administration of a single anoxic 1-liter breath has been well tolerated by subjects undergoing both ^{3}He MRI and ^{129}Xe MRI because for a single breath, the residual oxygen in the subject's lungs is sufficient to maintain blood O_2 saturation during the breath-hold. For each subject, their blood-oxygenation will be monitored throughout the time they are in the MRI scanner. If deemed necessary, supplemental O_2 will be provided by nasal cannula to maintain baseline O_2 satuation.

Incidental Findings - Anatomic ^{1}H MR images will not be routinely reviewed by a radiologist. However, if the technologist or study personnel note suspicious findings in the anatomic (^{1}H) images at the time of MRI, images from those subjects will be reviewed by a radiologist within 10 business days for incidental findings (tumors, hernias, aneurisms, etc). Such incidental findings will be communicated to the subject's physician. Copies of images will be made available to the subject's physician upon their request.

11. Costs to the Subject and Compensation: There are no additional costs to the subject for the MRI examination and the subjects will be compensated after each study visit for travel/parking and time for each study visit.

12. Data Analysis & Statistical Considerations: The primary objective of this study is to evaluate if the pulmonary function measured by MRI will worsen after radiation therapy compared to baseline. ^{129}Xe Ventilation images will be quantitatively assessed by semi-automated segmentation to determine their ventilation defect percentage (VDP). Similar metrics can be applied to ^{129}Xe gas exchange images, and ^{1}H perfusion images. Each of these images will have a corresponding defect score for exchange defect percentage (EDP), and perfusion defect percentage (PDP). Although we expect radiation therapy to exert a greater effect on gas exchange (EDP) and perfusion (PDP), the bulk of our experience to date is with the more well-established VDP metric. Thus, for the purpose of hypothesis testing and power justification, we chose VDP to be the primary endpoint for measuring the worsening pulmonary function after

radiation therapy relative to baseline. We have preliminary experience with this measurement in patients with idiopathic pulmonary fibrosis (IPF), which shares some functional similarities to radiation-induced pneumonitis. In 8 patients with IPF, we observe VDP=20.5+8.8 compared to 10 age-matched healthy control subjects with a mean VDP of 8.1+2.9.

We plan to enroll a total of 25 patients who undergo radiation therapy. Taking 20% attrition rate into account, the study will have a total of 20 treated patients who have VDP measures at both baseline and Visit 2 (at 10-14 weeks post RT). With valid VDP measures from 20 patients, the study has approximately 81% power to detect a 12% increase in VDP after RT at Visit 2 relative to baseline. This calculation assumes a one-sided significance level of 0.05 using a Wilcoxon Signed-Rank Test. These results are based on 2000 Monte Carlo samples and the assumption that the paired VDP measures follow a bivariate normal distribution with standard deviation 16 and correlation 0.2.

In addition to VDP, pulmonary functional images pre- and post RT will also be evaluated using the EDP and PDP metrics described above, as well as the regional differences in ^{129}Xe uptake in barrier tissues vs RBCs. Functional imaging maps will be co-registered with the patient's dose plan. Functional metrics such as RBC:barrier ratio will be computed in isodose regions and correlation plots will be generated.

The mean, standard deviation, median and range of VPD and other pulmonary function measures and the changes relative to baseline will be estimated for each visit at which MRI imaging is undertaken. The 95% confidence interval for means and averaged changes relative to baseline will be provided. The VDP increase 6 weeks after radiation therapy compared to baseline will be tested using Wilcoxon Singed-Rank test. To control overall type I error, formal hypothesis testing will not be conducted for the secondary endpoints for pulmonary functions. The trajectory changes of these endpoints over time and the dose-dependent damage effect will be evaluated using linear models for repeated measures. Point estimates and confidence intervals for relevant parameters will be provided for descriptive purpose. Appropriate transformation will be taken on these endpoints if normality assumption is clearly violated in the regression analysis.

13. Data and Safety Monitoring: Subjects will be monitored before, during and after each treatment with xenon to assess for adverse events and changes in vital signs. The parameters monitored include the following: subject assessment of anesthetic/analgesic effects, heart rate, and SPO2. The subjective sense of analgesia is assessed by an inquiring about how the subject feels after administration of the xenon dose. The subject will be asked to describe how they feel as well as about specific symptoms including: dizziness, light-headedness, numbness, euphoria, sleepiness, and tingling in extremities. Heart rate will be measured before and after each xenon treatment. Changes in heart rate of greater than +/- 20% are considered significant. If the subject is to receive another dose, the next dose will not be administered until the heart rate is within 20 % of its baseline value. If the subject has received their last dose, they will be observed until their heart rate is within +/- 20% of its base line value or until the end of the observation period,

whichever is longer. SPO2 is measured at baseline and after each xenon treatment. A decrease of SPO2 by greater than 5% is considered significant. If the subject is to receive another dose, the next dose will not be administered until the SPO2 is within 5 % of its baseline value. If the subject has received their last dose, they will be observed until the SPO2 is within 5% of its baseline value or until the end of the observation period, whichever is longer. The subject will be monitored for the duration of the xenon treatment and post procedural period by a qualified medical professional. If deemed necessary, supplemental O_2 will be provided by nasal cannula to maintain baseline O_2 satuation.

Discontinuation - Participation in this study is voluntary and subjects are free to withdraw at any time and for any reason. Furthermore, the individual subject will be withdrawn from the trial should they develop any worsening of health or new medical illness that is deemed to be a result of this study. Parameters to be evaluated include but are not limited to: shortness of breath, heart rate or decreased blood oxygenation related to xenon administration. If a subject experiences a decrease in oxygenation that is greater than or equal to 5% that persists for more than 5 minutes, and cannot be resolved by administering supplemental oxygen, they will be withdrawn from the trial. Similarly, if patients experience a change in heart rate of more than 20% on more than one occasion after xenon administration they will be withdrawn. Other reasons for discontinuation include subject becomes uncomfortable in the magnet, subject becomes unresponsive or is unable to protect their airway, subject requests study discontinuation, or other concerns.

If any subject experiences a serious adverse drug experience (as defined in 21 CFR Part 312.32(a)), the trial will be discontinued immediately.

This clinical research study will be monitored both internally by the PI and institutionally by the Duke Cancer Institute (DCI). In terms of internal review the PI will continuously monitor and tabulate adverse events. Appropriate reporting to the Duke University Medical Center IRB will be made. If an unexpected frequency of Grade III or IV events occur, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment, dose de-escalation, or potentially closure of the study. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled;
- Stopping rules for toxicity and/or response are met;
- Risk/benefit ratio is not altered to the detriment of the subjects;
- Appropriate internal monitoring of AEs and outcomes is done;
- Over-accrual does not occur;
- Under-accrual is addressed with appropriate amendments or actions;
- Data are being appropriately collected in a reasonably timely manner.

DCI review and monitoring of this protocol occurs in accordance with the NCI-approved Data and Safety Monitoring Plan. Briefly, protocol review begins with an initial review by the Cancer Protocol Committee (CPC), which assesses the ethics and safety of the protocol. Documentation of these assessments will be maintained. Formal, independent monitoring will be conducted by the DCI Monitoring Team after the first 3 subjects are enrolled, followed by annual monitoring of 1-3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk. DCI Monitoring Team reports and additional data/safety/toxicity reports submitted by the PI will be reviewed by the Safety Oversight Committee (SOC) on an annual basis. Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns. Monitoring visits may also be initiated upon request by DUHS and DCI Leadership, CPC, SOC, a sponsor, an investigator, or the IRB.

14. Privacy, Data Storage & Confidentiality: All consent and case report forms will be stored in a locked filing cabinet in the office of the study coordinator or principal investigator. Any other digital data (images, image analysis) will be associated only with the subject identification number and the date and time of the images. Image data will be retrieved and analyzed only by study personnel. The data is stored in a password protected, controlled access account with authentication and mandatory password change features. All CRF's will use the subject identification number as the only identifier. At the end of the study the key to the code will be destroyed.

Schedule of Events

Protocol Activities	**Screening (V0)[1]**	**Study Visit (V1)[1]**	**Study Visit (V2)[1]**	**Optional Study Visit (V3)[1]**
Informed Consent[1]	X			
Medical History	X	(X)		
MRI Screening Form	X	(X)	(X)	(X)
Pulmonary Function Testing[2]		X	X	X
Pregnancy Test[3]	(X)	(X)	(X)	(X)
MRI Session[4]		X	X	X
Subject monitoring and vital signs		X	X	X
Adverse events followup[6]		X	X	X
Hemoglobin (optional) Finger sensor machine	X	X	X	X

1. For most subjects, screening and study visit 1 will occur on the same day. However, these visits can be conducted separately if needed as long as it is completed before the initial RT treatment. Visit 2 will occur ten to fourteen weeks post RT. Optional Visit 3 will occur thirty-two to forty weeks post RT.
2. Pulmonary function testing will include one or more of spirometry, lung volumes, DL_{CO} and impulse oscillometry. For healthy volunteers taking part in the technical optimization part of the study, PFTs are not required, but may be collected if desired by the study team. If some or all PFT information is already available from the patient record and deemed sufficient by study personnel, PFTs may not be collected. Pulmonary function testing will be conducted at Duke Clinical Research Unit (DCRU). Key personnel will accompany the subject from the beginning through the completion of each study visit.
3. Any female patients of child-bearing potential scheduled for radiation therapy should have a negative pregnancy test per standard of care. However, if such information is not available, or for female healthy volunteers of child bearing potential participating for technicial optimization, a serum pregnancy test will be performed at screening. The test must be negative and the participant must agree to use an acceptable method of birth control for the duration of the study. Then a urine pregnancy test will be completed with a negative result before each MRI if the MRI is conducted on a different day than the screening visit or other study visits. The pregnancy test will be conducted and interpreted

by study personnel who have completed competency training from the Duke Office of Clinical Research (DOCR).

4. The MRI session will be conducted on the CAMRD research MRI scanner. Hyperpolarized ^{129}Xe is produced and delivered by the study team.
5. During the 1-hr MRI session, a qualified medical professional (MD, DO, PA, LNP, RN, RT or MT) will be on hand to monitor subjets during MRI and note any symptoms related to xenon MRI.
6. Based on the known pharmacokinetics of xenon, no additional effects are expected after subject is released from the imaging study. However, subjects will be provided contact information for the study coordinator so they can report any concerns over the 24 hours after undergoing MRI.