MSK PROTOCOL COVER SHEET

Prognostic Value of Tumor Hypoxia, as Measured by 18F-FMISO Breath Hold PET/CT, in Non-Small-Cell-Lung Cancer (NSCLC) Patients

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is an NCI funded (**U01CA157442-01A1**) study to assess the prognostic value of fluorine-18-labeled fluoro-misonidazole (^{18}F-FMISO), a hypoxia radiotracer, in patients with non-small cell lung cancer (NSCLC) who are treated with definitive conventionally fractionated radiation therapy (RT), neoadjuvant chemotherapy, or chemo-RT. The secondary goal will be to assess the predictive value of ^{18}F-FDG, a metabolic rate radiotracer, in a second group. Please note that all patients entered on this protocol will undergo the standard of care treatment for NSCLC. The information obtained from the use of investigational ^{18}F-FDG and ^{18}F-FMISO PET scans will NOT be used to manage patients' treatment on this protocol.

Schema:

There are two groups currently active in this protocol. Group 1 includes a mid-treatment FMISO PET scan and FDG PET scan. Group 2 includes a sequential injection of ^{18}F-FMISO and ^{18}F-FDG. Both groups will have completed a routine pre-treatment FB and breath-hold ^{18}F-FDG PET/CT and pre-treatment ^{18}F-FMISO PET Scan.

- Group 1: Perform a routine pre-treatment free-breathing (FB) and breath-hold (for only one PET Field of View, i.e. an additional ~10 min of PET/CT imaging) ^{18}F-FDG PET/CT. If the patient is planned to receive radiotherapy, the FB PET/CT scan will be used for RT planning.
- Group 2: Perform a routine pre-treatment free-breathing (FB) ^{18}F-FDG PET/CT. If the patient is planned to receive radiotherapy, the FB PET/CT scan will be used to RT planning.
- Both groups with perform a pre-treatment dynamic ^{18}F-FMISO PET scan (^{18}F-FMISO1). This scan will occur at least one day after the baseline ^{18}F-FDG PET/CT scan, but prior to initiation of therapy. A baseline ^{18}F-FDG PET/CT scan may be acceptable provided it is not earlier than one month prior to the ^{18}F-FMISO study and will assist to define the field of view of the dynamic ^{18}F-FMISO PET scan. If a CT is available to allow definition of the tumor region, then the ^{18}F-FMISO may be performed before the FDG PET scan. Dynamic ^{18}F-FMISO PET images will be corrected for breathing-induced artifacts allowing kinetic analysis to be performed for both the motion-corrected and the free-breathing dynamic PET image sets. The degree of hypoxia within the tumor volume will be estimated by the magnitude of the ^{18}F-FMISO irreversible trapping rate constant.

- **Group 1 : 18F-FMISO2/FDG mid-treatment PET/CT**: Perform a mid-treatment dynamic ^{18}F-FMISO (FMISO2) PET/CT (following the same protocol as for the baseline FMISO) scan in a group of twenty five patients, undergoing RT or concurrent chemo-RT. This scan will occur two weeks +/- 4 days after the start of radiotherapy or the radiation portion of combined chemo-radiation (Diagram 1).

- Perform a mid-treatment ^{18}F-FDG PET/CT scan in a group of twenty five patients, undergoing RT or concurrent chemo-RT. This scan will occur two to three weeks +/- 4 days after start of treatment of radiotherapy or the radiation portion of combined chemo-radiation.^{18}F-FDG PET/CT scans will be performed in both Free-Breathing (FB) and Breath-Hold (BH) modes. The predictive value of ^{18}F-FDG, based on the change in lesion SUVpeak between baseline and the 3-week mid-treatment

scan and following the PERCIST criteria, will be assessed using both the FB, and the BH, image sets independently. Results deduced from the FB and BH data sets will be compared and correlated with outcome.

- **Group 2: Combined 18F-FMISO/18F-FDG baseline PET/CT:** In a group of 5 patients, two PET radiotracers ^{18}F-FMISO and ^{18}F-FDG will be injected sequentially into the patient. Since all PET radiotracers emit the same 511 keV coincidence photons, it is not possible to discriminate events from these different radiotracers. However, by conducting a dynamic PET/CT scan with staggered ^{18}F-FMISO and ^{18}F-FDG injections (45min +/- 15min apart), the kinetic profiles should provide sufficient information to allow signals from the two radiotracers to be clearly separated. This sequential ^{18}F-FMISO / ^{18}F-FDG study will be performed at least one day after the sole FMISO1 radiotracer baseline PET/CT scan, and prior to the initiation of therapy. The ^{18}F-FMISO and ^{18}F-FDG individual signals will be deduced from the combined dynamic PET images by means of kinetic modeling, and the corresponding radiotracers entrapments within the tumor will be determined. The accuracy of the ^{18}F-FMISO signal extraction from the combined one in the staggered ^{18}F-FMISO/^{18}F-FDG dynamic PET/CT study will be assessed by comparison to that deduced from the sole FMISO1 study (Diagram 2).

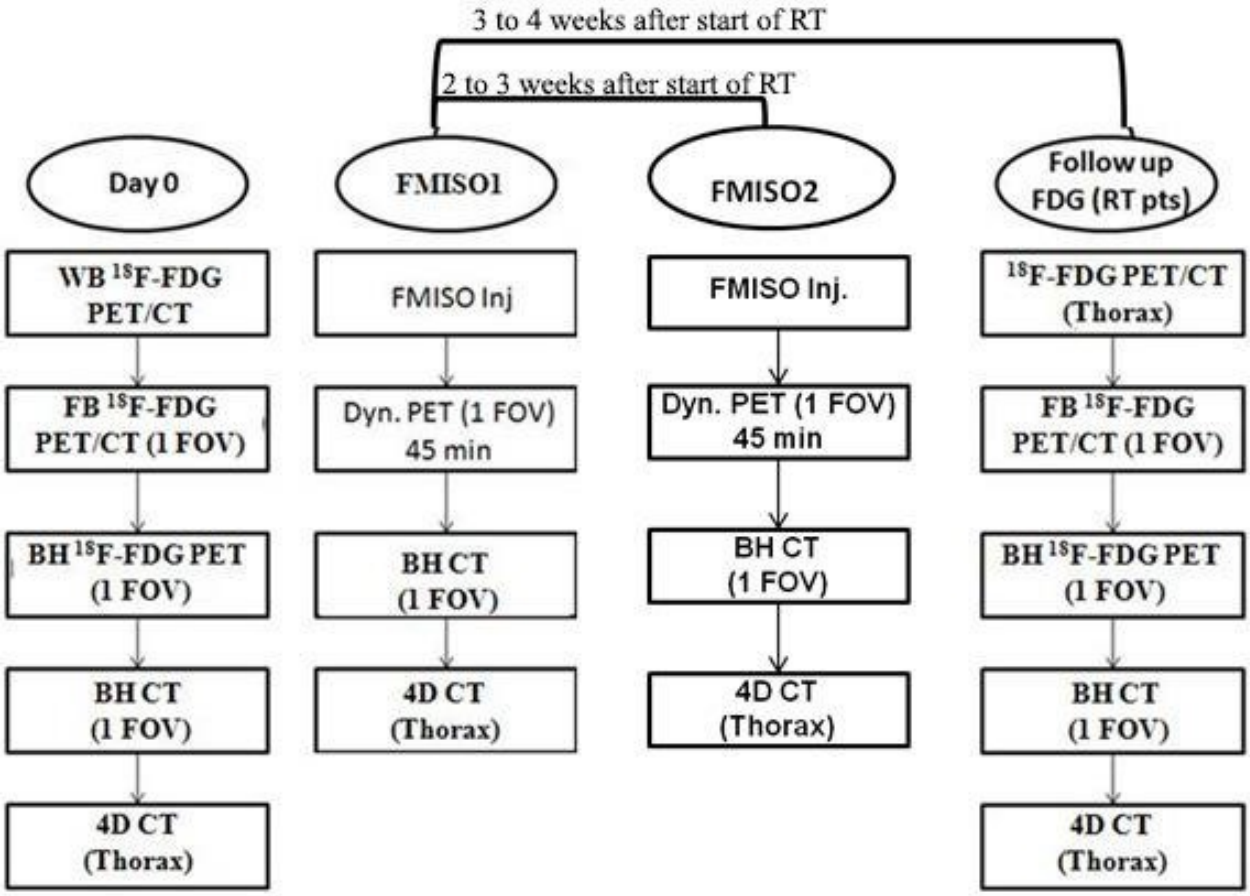


Diagram 1. **Combined 18F-FMISO/18F-FDG baseline PET/CT**

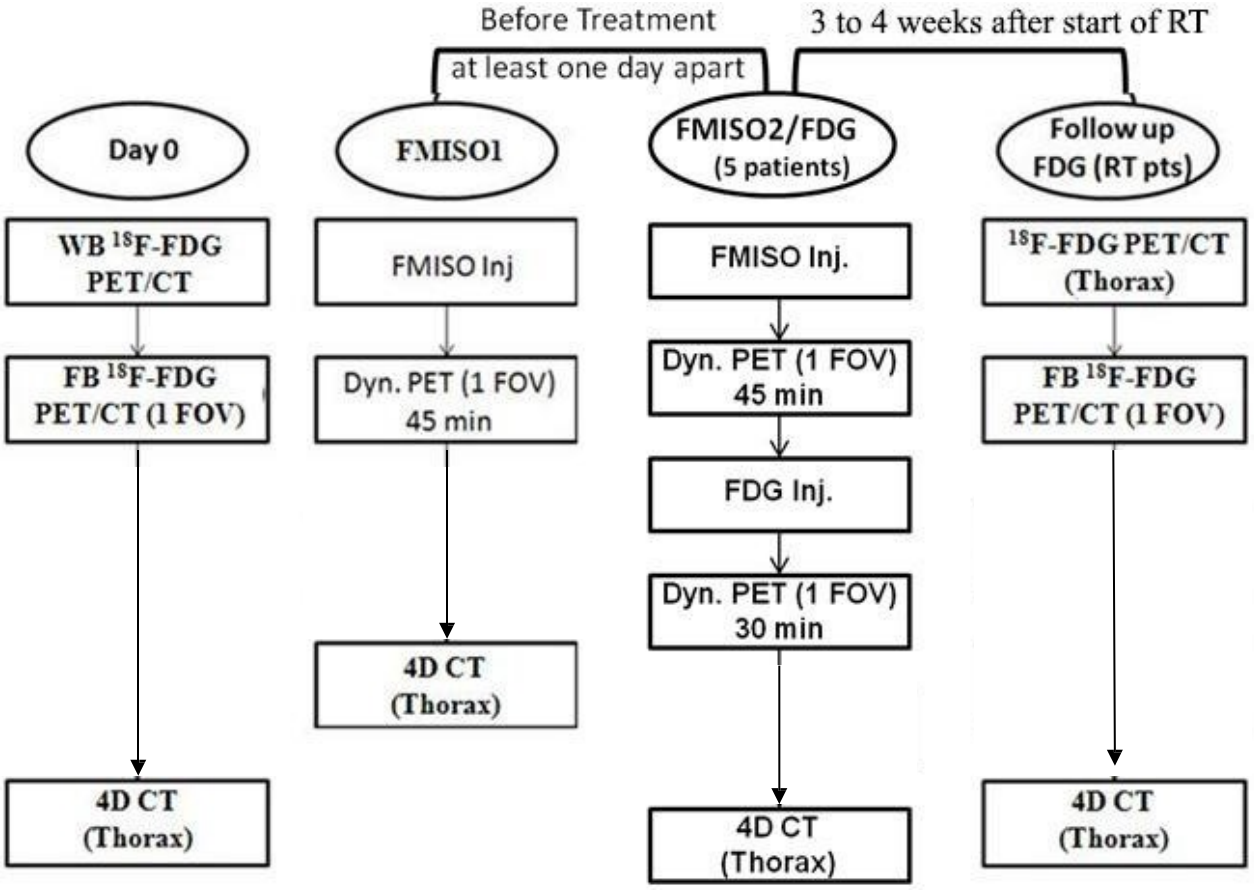


Diagram 2. Group 2: Sequential FDG and FMISO treatment group

2.0 OBJECTIVES AND SCIENTIFIC AIMS

The primary objectives of this study are:

- To correlate the presence and extent of hypoxia, as defined by ^{18}F-FMISO FB and BH PET/CT at baseline with 3-year progression-free survival (PFS) and overall survival (OS).

- To assess the predictive value of ^{18}F-FMISO PET/CT in lung cancer patients undergoing radiotherapy or concurrent chemoradiotherapy, as measured by Breath-Hold (BH) and Free-Breathing (FB) PET/CT images, and to determine whether BH PET/CT provides greater predictive capability than Free-Breathing (FB) PET/CT.

The secondary objective of this study is:

- To assess the predictive value of ^{18}F-FDG PET/CT in a group of twenty five lung cancer patients undergoing radiotherapy or concurrent chemoradiotherapy, as measured by Breath-Hold (BH) and Free-Breathing (FB) PET/CT images, and to determine whether BH PET/CT provides greater predictive capability than Free-Breathing (FB) PET/CT.

- To assess the feasibility of simultaneous ^{18}F-FDG and ^{18}F-FMISO PET dynamic acquisitions in a group of 5 patients undergoing radiotherapy or concurrent chemoradiotherapy. If successful, our approach would allow multi-radiotracer PET exams on the same day reducing the need for extra patient visits. For the patients who will undergo the dual FMISO/FDG study, the mid-treatment FMISO will be optional.

3.0 BACKGROUND AND RATIONALE

3.1 ^{18}F-FDG PET/CT

^{18}F-FDG PET is a non-invasive molecular imaging tool that has been shown to have a major impact on the diagnosis and staging of NSCLC, as well as in treatment planning of radiotherapy and detection of recurrent disease (*1-4*). Its prognostic and predictive values in NSCLC have been well demonstrated (*5*)

In a pilot study that included 15 patients, a reduction in ^{18}F-FDG uptake of more than 50% between pre- and post- induction chemotherapy in the primary tumor or mediastinal clearance was shown to be a better predictor of long-term survival (*6*) compared with the standard WHO criteria used for response assessment on CT. In another multi-center study that evaluated ^{18}F-FDG-PET before and after 1 and 3 cycles of induction chemotherapy the residual metabolic rate of glucose after completion of induction chemotherapy appeared to be the most prognostic factor (*7*). Its predictive value with respect to therapy outcome of combined chemo-radio therapy has also been demonstrated (*8-10*). Currently, no early markers of tumor response to radiation therapy are in existence or in clinical use. While FDG-PET has become a standard modality for staging and re-staging of NSCLC, its value as an early response marker during radiation therapy remains unclear. The University of Michigan tested the value of a mid-treatment FDG-PET scan at 45 Gy in 15 patients (*11*). The qualitative response during RT correlated with the overall response post-RT. However, the later during the treatment course the PET scan is performed, the lesser are the chances of making adjustments to the initial first-line treatment, as the majority of the RT dose is already delivered at 45 Gy. Therefore, we are planning to perform the FDG-PET scan at an earlier time point of 3 weeks at a dose of approximately 30 Gy. This will provide the basis for early tumor assessment and adaptive radiation therapy strategies that would take into account an early tumor response. It would allow stratification of patients into favorable and unfavorable responders and the development of individually tailored strategies for these patients.

Consequently, ^{18}F-FDG-PET can form the basis for clinical trials evaluating the feasibility of adopting therapy based on response assessment (*12-15*).
Due to patient breathing, FDG PET quantitation may become susceptible to breathing-induced uncertainties, which may reduce the prognostic and predictive values of FDG-PET. Breath-Hold PET/CT acquisition has been shown to improve the accuracy of PET quantitation. In contrast to the study by Kong et al. (*11*), we will therefore measure the prognostic and predictive values of FDG PET using BH PET data, and compare those with results deduced from the free-breathing data sets. Due to the improved accuracy of BH-PET quantitation, we expect BH data would yield improved prognostic values over those of the FB PET.

3.2 Hypoxia

Hypoxia is a characteristic feature of malignant tumors that has been well established (*16-22*) . Unlike healthy tissues, tumors often grow at a rate that outgrows their blood supply resulting in the emergence of regions of hypoxia. Immunohistochemical studies have shown nests of hypoxic cells of up to several hundred micrometers in diameter, located at poorly perfused locations within the tumor (*23-25*). Hypoxia can create selective pressures that render the tumor more aggressive and radioresistant, and has been shown to exhibit an increased likelihood of locoregional recurrence, propensity for metastasis, and poor overall outcome. With invasive measurements, a hypoxia fraction HF2.5 (percentage of measurements <2.5 mmHg) was shown to be the most predictive factor for survival in head & neck cancer (HNC), with a threshold HF2.5 of 20% [17]. In NSCLC, 62% of patients exhibited a HF2.5 < 20% (*26*).

Locoregional control in non-surgically treated NSCLC patients continues to be a major challenge. Locally-advanced NSCLC patients currently experience freedom from local progression at 3 years (FFLP, defined as intrathoracic tumor progression by World Health Organization criteria) of only 38% and locoregional control (LRC, a stricter definition that requires at least a partial response prior to progression) of 14%, with a 5-year overall survival of approximately 20%, as it was recently demonstrated in a comprehensive review of seven RTOG trials (*27*). This may at least in part be due to the often large tumor size and significant hypoxia levels in these tumors. PET is a noninvasive imaging modality with the potential to identify tumor hypoxia at both global and local levels through the use of hypoxia targeting molecules. If these hypoxic regions are identified, this will lay the foundation for future studies targeting these hypoxic sub-regions and/or altering treatment regimen, with the ultimate goal to improve the treatment outcome of patients with NSCLC. We and others have previously shown that dose escalation can be successfully given to patients with stage III NSCLC to a maximum tolerated dose (MTD) of 84 Gy (*28*). This resulted in a promising 2-year local control rate of 52%. RTOG 0117, a phase I/II dose escalation study in patients treated with concurrent chemoradiation, found the MTD to be 74 Gy (*29*). A pooled analysis of seven RTOG studies of chemoradiation for locally advanced NSCLC found that a 1-Gy increase in biologically effective dose resulted in an approximately 4% relative improvement in survival and a 3% relative improvement in locoregional control (*30*). Currently, the standard dose for concurrent chemoradiation therapy is 60 Gy. While a recent phase III study (RTOG 0617) appeared to be unsuccessful when escalating the dose to the entire tumor volume to 74 Gy (*31*), it remains unknown whether escalating the dose to radioresistant tumor subvolumes would not result in better tumor control. Therefore, identifying such subvolumes may provide the basis to a more intelligent dose escalation approach in order to improve the dismal outcomes in stage III NSCLC.

3.3 ^{18}F-FMISO PET Scan and Tumor Hypoxia

Positron emission tomography with ^{18}F-Fluoromisonidazole (^{18}F-FMISO PET) is a non-invasive imaging technique that was shown to be clinically feasible for detecting tumor hypoxia in NSCLC (*32, 33*). Patients will be given the option to participate in a research study that aims to investigate the prevalence of hypoxia (as determined by ^{18}F-FMISO PET) in this patient population, and to assess the reproducibility and prognostic value of ^{18}F-FMISO dynamic PET (dynPET) images in NSCLC patients prior to standard treatment for their lung cancer. Tumor hypoxia is an independent predictor of poor

prognosis in several types of cancer, including NSCLC. Hypoxia imaging may be of particular interest in NSCLC, because it is relatively common in lung cancer, and because the outcome for hypoxic tumors may potentially be improved with more aggressive chemotherapy or radiotherapy, or hypoxia-directed treatments such as the administration of hypoxia activated prodrugs (*34, 35*) or carbogen breathing (95% oxygen, 5% carbon dioxide) (*36*). ^{18}F-FMISO PET has been shown to correlate with hypoxia and treatment outcome in NSCLC (*32, 37*). Previous study used either qualitative analysis of the dynamic FMISO time activity curves (*38*) or quantitative analysis of late static FMISO images (*37*) to identify hypoxia.

The optimal method to quantitate hypoxia using ^{18}F-FMISO is to perform compartmental analysis of the dynPET images (*39-41*). This is a method which uses kinetic information from dynamic scans to assess the rate of uptake and entrapment within the hypoxic tumor tissue. However, compartmental analysis is not meaningful on standard clinical PET images of the lung because of respiratory motion during the PET acquisition. Our group at MSKCC has developed a technique for Breath-Hold (BH) PET/CT imaging. During BH PET/CT, patients are asked to hold the breath for as long as possible, and data are acquired only during the time of the BH, using an in-house respiratory tracking device to monitor patient breathing motion (*42*). PET emission data will be acquired only while the patient is holding the breath as monitored by an external camera and chest sensor. This process will be repeated until a total of 3 min of BH PET data (equivalent to clinical setup) are acquired. We now propose a novel technique to acquire motion-free ^{18}F-FMISO dynPET images of lung (one 15 cm field of view) to make accurate compartment analysis, and thus quantification of tissue hypoxia, possible. We shall acquire clinical ^{18}F-FMISO dynPET images in Free-Breathing (FB) with the list mode (LM) option. During the dynamic PET study, the patient's breathing signal will be recorded simultaneously using an in-house developed tracking software assisted by a video camera. The camera is used to monitor the motion of fiducial markers positioned on the patient's abdomen. The patient's breathing signal will be correlated to the PET data on an event-by-event basis and then only those corresponding to end-expiration will be selected for the final PET images, thus resulting in motion-free images. Incorporating all the PET events from the same dynamic PET study results in the FB dynamic PET data set.

In PET/CT, CT images are used to correct for attenuation in the PET images. Spatial matching between PET and CT images is therefore crucial. Therefore, CT images at breathing phases matching those of the PET images will be acquired. PET data will be corrected for attenuation using the phase-matched CT images.

The value of ^{18}F-FMISO-PET as an early response marker during radiation therapy is still unknown. In a study in 20 patients with head and neck cancer who underwent baseline and mid-treatment FMISO imaging, 90% of patients showed complete resolution of ^{18}F-FMISO uptake in the mid-treatment scan, suggesting tumor re-oxygenation (*43*). In the current study, we will assess the predictive value of ^{18}F-FMISO at 2 weeks +/4 days post-initiation of therapy (~ at a dose of 20Gy). This will allow identification of persistent radioresistant tumor sub-volumes. These data may provide the basis for future response adaptive radiation therapy strategies. For instance, patients with persistent hypoxia, if prognostic of poor outcome, may in a future studies be selected for a site directed additional radiation boost.

In this protocol, both ^{18}F-FMISO and mid-treatment ^{18}F-FDG imaging shall be used for exploratory research purposes only; the image findings and results will not be used to change patient management. MSKCC holds an IND for the use of ^{18}F-FMISO under IRB protocol #04-070 (P.I. Dr. Nancy Lee).

This protocol shall use ^{18}F-FMISO under cross-file with IND 115764, since the radiolabeling chemistry and dosage shall be identical to protocol IRB #04-070.

3.4 Simultaneous imaging of tumor hypoxia and tumor metabolism

Imaging hypoxia and metabolism simultaneously may provide a new understanding of the role of the tumor microenvironment; in particular the interplay between hypoxia (defined by ^{18}FMISO) and tumor cell metabolism (defined by ^{18}FDG).
^{18}F-FMISO and ^{18}FDG have been shown to be important prognostic and predictive biomarkers in patients undergoing CRT [59, 60]. Identifying simultaneously hypoxic and metabolically active sub-regions within the tumor is a more coherent measurement of the tumor microenvironments than co-registering images acquired in different imaging sessions where temporal changes in the biology and inaccuracies in the image registration curtail the integrity of the data. Previous studies have demonstrated both the feasibility and potential for simultaneous assessment of two physiological processes (mainly in brain) by exploiting temporal [61] kinetic, or daughter outputs (positron vs positron+cascade γ) (*44*) differences between radiotracers.
In this protocol, we are going to apply a new method to obtain the information from two F-18 based PET radiotracers (^{18}F-FMISO and ^{18}FDG) in a single PET/CT acquisition. We have developed a preliminary means of decoupling the individual signals with the ultimate goal to use the combined hypoxia/metabolic rate map to guide and adapt CRT, and monitor response in a larger cohort of patients with NSCLC and other malignancies. In preliminary studies, we have successfully established methodology and validated that in both mathematical simulations and animal models, for achieving this objective, and propose to apply this methodology to patients receiving sequential ^{18}F-FMISO and FDG dynamic PET exams in this study. We propose to conduct compartmental analysis from a single dynamic ^{18}FMISO and ^{18}FDG PET acquisition in which ^{18}FMISO is injected concurrently with the start of the dynamic PET acquisition, followed by an injection of ^{18}FDG about 45 min +/- 15 min later. We *hypothesize* that simultaneous ^{18}FMISO and ^{18}FDG PET imaging will result in prognostic and predictive values that are superior to those achieved when imaging is performed separately for each radiotracer (i.e. in 2 scanning sessions, days apart). We believe this enhancement will be due to (1) exact co-localization of the 2 markers (no co-registration necessary), and (2) absence of inter-scan transient biologic changes. We believe this method will lay the foundation for future studies using dual PET radiotracers in patients with NSCLC and other malignancies, and may have potential implications for dose painting strategies in radiotherapy, adaptive CRT, and assessing response to treatment. If clinically feasible, comparison of the prognostic and predictive values of combined ^{18}F-FMISO/^{18}F-FDG with those of each of the two radiotracers (when imaged separately) shall be the subject of a future investigation in a larger cohort of lung patients.

3.5 Respiratory Motion in PET/CT imaging of the thorax

Patient's respiratory motion during PET/CT imaging results in artifacts in the PET/CT images due to internal organ motion. In CT images, breathing-induced artifacts are mainly due to the dynamic interaction between transaxial image acquisition and the asynchronous motion of tumor and normal tissue (*45*). Commonly observed artifacts include distortion of the dome of the liver at the lung-diaphragm interface, splitting of a tumor into multiple distinct parts, out-of-order shuffling of the transaxial slices, and creation of discontinuities in the diaphragm/lung interface (*45*). In PET, due to

the long acquisition time per bed position (3 to 7 min), PET images are then time-averaged over many breathing cycles (average breathing period is 5 seconds). This results in the blurring of the target volume (*42, 46, 47*), and reduces the apparent radiotracer uptake (*46, 48*).

In hybrid PET/CT, respiratory motion can result in hybrid motion artifacts, primarily due to the temporal mis-match between PET images and the corresponding CT-based attenuation map. A common artifact due to the tempo-spatial mis-match between PET and CT is the mis-localization of lesions at the border of two organs (*42, 49*). The tempo-spatial mismatch between PET and CT images can also result in an increased uncertainty in the apparent tumor SUV due to the use of a non-spatially matching CT image set to correct for attenuation in the PET images. Erdi and co-workers showed dependence of the measured tumor SUV on the breathing phase at which CT images were acquired at.

3.6 Correction for Respiratory Motion Artifacts: Deep-Inspiration-Breath-Hold (DIBH) PET/CT

We have recently developed a novel technique to correct for breathing artifacts in PET/CT images, the Deep-Inspiration-Breath-Hold (DIBH) acquisition(*42*). We believe DIBH is the most pragmatic and robust approach to eliminate misregistration of PET and CT data. In this approach, the patient is instructed to hold the breath during CT acquisition. The amplitude at which the hold (HA) period occurs is identified using a respiratory tracking system. During PET acquisition, the patient is then instructed to hold the breath at the same (HA), over subsequent periods. PET data will be acquired only while the patient is holding the breath as monitored by an external camera and chest sensor. This will repeated till a total of 3min of BH PET data are acquired. Finally, PET data corresponding to the hold periods are summed into one data set, and then reconstructed using the corresponding breath-hold CT image set. With DIBH PET/CT (as compared to nonrespiratory motion-corrected PET/CT) we observed as much as an 83% increase in lesion SUV, and as much as 50% improvement in spatial matching between PET and CT(*42*). DIBH PET/CT had the advantage of reducing misregistration, as both the CT and the PET components were acquired in the same respiratory phase. This was particularly useful for distinguishing between pulmonary and extrapulmonary lesions in the chest wall or mediastinum. Additionally, a small nodule that was not seen on clinical PET/CT showed mild ^{18}F-FDG uptake on BH PET/CT; this was an additional site of metastasis in a patient with lymphangitic spread. DIBH-PET also results in an improved signal-to-noise ratio, which can yield increasing lesion detectability. In CT, DIBH imaging also resulted in detection of 2.2 additional nodules on average per patient, especially when those nodules were smaller than 0.5 cm(*50*). DIBH CT also allowed more precise localization and characterization of pulmonary lesions than non-DIBH CT(*42, 50*).

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a single-institution exploratory study evaluating the prognostic and predictive significance and reproducibility of tumor hypoxia as imaged by ^{18}F-FMISO PET, in NSCLC patients before receiving any treatments for their disease. In a sub-group of these patients, we will assess the predictive value of ^{18}F-FDG PET/CT as well. Moreover, in a sub-group of five patients, we will assess the feasibility of simultaneous ^{18}F-FMISO/^{18}F-FDG acquisitions. Patients will be identified in thoracic oncology, radiation oncology, or radiology departments at the time of their planned diagnostic imaging studies.

We will also evaluate the pharmacokinetic properties of ^{18}F-FMISO during the imaging studies. Moreover, we will evaluate the significance of breath hold (BH) imaging over standard techniques in both^{18}F-FDG PET/CT and ^{18}F-FMISO PET/CT image sets in patients from Group 1, as outlined in Sections 9.1 and 9.2. Patients will be identified and consented prior to their baseline ^{18}F-FDG-PET/CT. A total of 25 patients will be accrued for this study over a 3 year period; 10 patients who are receiving RT or concurrent chemo RT and 16 patients who are receiving neoadjuvant chemotherapy. The group of 10 patients receiving RT or concurrent chemo-RT will receive an additional repeat ^{18}F-FDG PET/CT scan at mid-treatment.

4.2 Intervention

All enrolled patients will undergo a baseline ^{18}F-FDG PET scan as part of their standard clinical treatment for NSCLC. Dynamic ^{18}F-FMISO PET scans will be performed on one of the GE PET/CT scanners in 3D mode, at least one day after the baseline ^{18}F-FDG PET scan. The dynamic baseline 18F-FMISO studies may precede the ^{18}F-FDG study if the patient had a CT or PET/CT scan within the last 30 days that would permit the investigators to localize the tumor of interest during the ^{18}F-FMISO study. In a group of 5 patients, the feasibility of simultaneous imaging of ^{18}F-FMISO and ^{18}F-FDG will be assessed. The patient will have an IV line placed for radiotracer injection and for venous blood sampling. All dynamic PET scans will be performed over one PET FOV centered at the lesion position. The ^{18}F-FDG mid-treatment PET/CT scan will be performed over only one bed position at the times identified in section 1.0.

The studies outlined in Section 9.0 are the intervention. These research study results will not impact clinical care which will be left to the discretion of the treating physician. Patients will be followed with CT scans of the chest every 3-4 months in the first three years as per standard clinical care. Available data will be used for radiologic progression of disease and survival.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

F-18 labeled F-misonidazole is prepared and tested for quality assurance in this study at MSKCC or by an equivalent qualified supplier. The radiopharmaceutical is being utilized in this protocol under a MSKCC IND. Bio-distribution data on ^{18}F-MISO are summarized in section 11.2.3.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Pathologic confirmation of NSCLC at MSKCC
- No prior treatment for this diagnosis of NSCLC
- Patient to be treated with neoadjuvant chemotherapy or patient to be treated with definitive RT, sequential chemo-RT, or concurrent chemo-RT (minimum dose of 50 Gy in 25 fractions)
- Tumor must measure ≥ 2cm on CT
- Age ≥ 18 years
- Ability to hold the breath for 10 seconds
- Karnofsky performance status ≥ 70%

- Women of childbearing age must have a negative blood pregnancy test

6.2 Subject Exclusion Criteria

- Women who are pregnant or breast-feeding
- Severe diabetes (fasting Blood Glucose > 200 mg/dl)

7.0 Recruitment Plan with limited waiver of authorization

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treatment physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

Patients who are receiving chemotherapy only will be identified when they are referred to Nuclear Medicine for their standard FDG PET scans. Patients receiving combined chemoradiotherapy will be identified by the treating Radiation Oncologist when they are assessed in the Radiation Oncology clinics.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached.

As participating in this protocol is not intended to provide any clinical benefit to the patient, patients will receive a stipend for their time. At the completion of their study participation, patients will receive a check for up to $200, which is $100 per completed FMISO scan session. If the patient does not complete both scan sessions, the stipend which they receive will be prorated for the number of sessions completed.

8.0 PRETREATMENT EVALUATION

Patients must have the following tests or procedures prior to receiving any protocol scans.

- Histological confirmation of Non-Small Cell Lung Cancer at MSKCC
- Review of medical history and current medications
- Physical examination
- Pregnancy test for women of childbearing potential
- Standard clinical scans:
    - ^{18}F-FDG PET Scan performed at MSKCC
    - CT scan of the chest

9.0 TREATMENT/INTERVENTION PLAN

Patients will be monitored by a member of the nuclear medicine staff before, during and through the completion of their imaging studies.

9.1 ^{18}F-FDG PET/CT:

In patients who have consented to this study prior to their baseline ^{18}F-FDG PET scan, 4D-CT (10 mA)/free breathing PET and breath hold CT(10 mA)/PET images will be acquired over one field-of-view encompassing the lesion in the ^{18}F-FDG PET/CT scan in order to assess the improvement in the prognostic value of ^{18}F-FDG-PET/CT in lung cancer due to correction of breathing-induced artifacts in the PET/CT images. The PET/CT acquisition will be assisted by an in-house developed respiratory tracking software and video camera to monitor the patients breathing motion, and then correct for breathing–induced artifacts in the PET/CT images. The patient breathing during all phases of the study will be monitored and recorded by the respiratory tracking device. Such respiratory tracking allows events captured by the PET scanner to be associated with different phases of the respiratory cycle. The baseline and follow-up ^{18}F-FDG PET/CT scans for each individual patient should be performed on the same PET/CT scanner for consistency purpose. For patients receiving radiation therapy or concurrent chemo-RT, this research procedure will immediately follow the standard radiotherapy ^{18}F-FDG PET/CT simulation protocol, with the patient in treatment position. This group will also receive a mid-treatment ^{18}F-FDG PET/CT scan which will occur three weeks +/- 4 days after start of treatment of radiotherapy or the radiation portion of combined chemo-radiation. This mid-treatment ^{18}F-FDG PET/CT is investigational. Only patients in Group 1 will participate in BH scans.

All research scans will be performed by the Nuclear Medicine team. For patients receiving radiation, all ^{18}F-FDG PET/CT scans will be performed on the GE PET/CT scanner residing in the radiotherapy simulation suite. Otherwise, those scans will be performed on one of the GE PET/CT scanners residing in nuclear medicine.

9.2 ^{18}F-FMISO PET/CT Scan Protocol:

The first ^{18}F-FMISO PET/CT scan will be performed within 14 days (+/- 5 days) after the baseline ^{18}F-FDG scan, and before starting therapy. Dynamic FMISO PET scans will be performed on one of the GE Discovery PET/CT scanners residing in the nuclear medicine department at MSKCC. The patient will be set up in treatment position with intra-venous lines for radiotracer injection and for venous blood sampling. One 370 MBq (10 mCi) +/- 10% dose of ^{18}F-FMISO will be injected as a bolus, and the dynamic scan initiated coincident with the injection.

Dynamic ^{18}F-FMISO PET data will be acquired in List Mode and reconstructed in time frames that display the kinetics of tumor uptake. The total duration of the study is approximately 3 hours. The patient is injected in the PET scanning position on the couch and PET data acquired from 0-40 min. The patient is then allowed to return to the waiting room and rest. There are two further scan segments at approximately 90 min and 180 min post injection each of 10-minute duration. The total PET scan time within the 3 hour imaging session is therefore only 60 minutes. No further radioactivity will be injected for the 2nd and 3rd PET scan segments. In all three sessions of the dynamic PET study, the patient's breathing signal will be recorded simultaneously using the in-house developed tracking described previously. The respiratory signal will be used to retrospectively identify those PET events that occurred at end-expiration. Those events will be selected retrospectively to generate a dynamic PET data set corresponding to end-expiration (BH-dyn PET), motion-free PET images.

In each of the three dynamic sessions, a 4D-CT (10mA) scan and a BH-CT (10mA) scan (at end-expiration) of a 15cm segment of the body (the field of view of the PET scanner) will be performed with the tumor at the field center. These images will be used for both attenuation correction and registration of the serial image set, for the free-breathing and BH PET dynamic data sets respectively.

To further facilitate patient image registration, external fiducial markers may be placed on the patient's thorax.

A second set of three dynamic ^{18}F-FMISO scans will be performed following the same sequence as outlined above for the baseline dynamic ^{18}F-FMISO study, at 2 to 3 weeks (+/- 4 days) post-initiation of therapy.

To ensure patient safety, vital signs and toxicity assessments will be performed immediately after each scan session. Additionally, approximately 24 hours (or on the next business day) after the completion of each scan session, a toxicity assessment will be completed via a telephone followup.

Only patients in Group 1 will participate in BH scans.

9.3 Pharmacokinetic Modeling of ^{18}F-FMISO PET:

The dynamic data of the 18F-FMISO radiotracer in the tumor must be supplemented by clearance data from the blood. Blood samples may be taken at pre-designated times during the 18F-FMISO PET scan. If the PET images contain the heart within the field of view, one IV blood sample (about 1-2 ml) will be drawn at 30-40 minutes post 18F-FMISO injection. If the heart is not within the PET FOV,a maximum of 9 IV blood samples (about 1-2 ml each) may be obtained at approximately the following time points: 1, 2, 3,4, 5, 15, 30, 90 and 180 minutes post injection. A separate IV line (other than the one used for FMISO injection) will be used to draw the blood. These samples will be weighed and counted for the purpose of determining the blood clearance kinetics and the tumor input function.

Compartmental kinetic analysis of the dynamic ^{18}F-FMISO PET images will be conducted using the blood clearance time activity curve as input function to the ^{18}F-FMISO compartmental model. The kinetic rate constants k1, k2, and k3 (trapping rate) will be deduced. As a first approximation, hypoxic sub-regions within the tumor will be defined based on a k3 > 0.1. We will then re-assess this k3 threshold based on results from the first 12 patients.
The same kinetic analysis will be repeated for the 2nd baseline ^{18}F-FMISO study. The kinetic rate constants from the first and second ^{18}F-FMISO studies will be compared, as well as the geographic positions of the hypoxic sub-volumes within the tumor between the first and second scans.

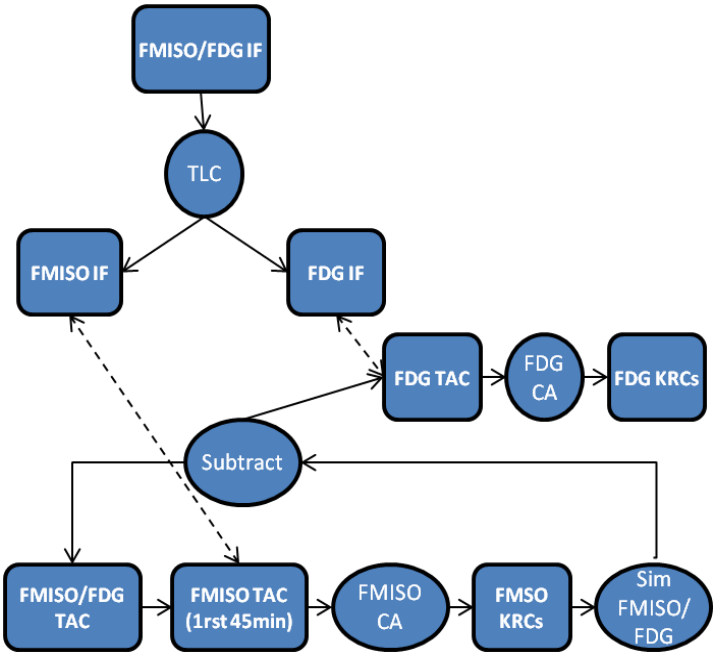
9.4 Simultaneous ^{18}F-FDG/^{18}F-FMISO PET/CT Scan Protocol:

Simultaneous Dynamic PET ^{18}FMISO/^{18}FDG scan will be performed at least one day after the sole baseline ^{18}FMISO PET/CT, but preceding chemo- or radiation therapies. Dynamic PET/CT data will be acquired over the same single FOV as for the sole baseline ^{18}FMISO PET/CT described above. CT images will be acquired for PET attenuation correction purpose. Imaging will start simultaneously with the intravenous bolus injection of ^{18}F-FMISO (8 mCi +/- 10%). PET data will be acquired in list mode (LM). The dynamic acquisition will last for up to a total of 120 min. 8 mCi (+/- 10%) of ^{18}FDG will be injected intravenously 45 min +/- 15 min after the ^{18}F-FMISO injection, and without interruption of the dynamic PET acquisition. One additional 10 min dynamic PET scan will be performed at 180 min post-FMISO injection. If the patient cannot tolerate the length of the first imaging session, an additional 10 min dynamic PET scan may be performed at 90 min +/- 10 min. Blood samples may be withdrawn following the same protocol as for the sole FMISO dynamic study described above.
For each of the imaging sessions a 4DCT at 10mA and a CT-BH (40mA and 1-mA for the first session and the subsequent sessions respectively) will be performed for attenuation correction,

All PET and CT data will be acquired and recorded in a secure patient database. During all imaging sessions, patients will be immobilized in RT alpha cradle if available and tolerable.

9.5 Pharmacokinetic Modeling of Simultaneous ^{18}F-FDG/^{18}F-FMISO PET:

We will perform compartmental analysis of the combined ^{18}F-FMISO/^{18}F-FDG tumor uptake profiles obtained from dynamic PET images. The individual ^{18}F-FMISO and ^{18}F-FDG input functions will be derived from the drawn blood samples during the dynamic PET study, using Thin Layer Chromatography (TLC), and based on methodology we have previously developed. We have previously shown the feasibility of this technique to uncouple^{8}F based radiotracers, ^{18}F-FMISO and ^{18}F-FLT. We will use the same technique here to uncouple the FMISO/FDG fractions in the blood. The tumor combined FMISO/FDG Time Activity Curve (TAC), will be determined from the dynamic PET image set, and then the ^{18}FMISO and ^{18}FDG respective output functions will uncoupled from the combined TAC. Finally, compartmental analyis will be carried out for the FMISO and FDG respective output functions The kinetic parameters $V_{□□□□1}$, k_2, k_3, and k_4 (for ^{18}FDG) will be calculated for the FMISO and FDG signals respectively. The procedure for carrying out compartmental analysis of FMISO and FDG dynamic PET with both radiotracers imaged within the same PET imaging session is shown in diagram 3.



- TLC: Thin Layer Tomography
- IF: Input Function
- TAC: Time Activity Curve
- CA: Compartmental Analysis
- KRC: Kinetic Rate Constant
- Sim: Radiotherapy Simulation

Diagram 3.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

There will be no specific monitoring after the studies. All patients will be evaluated according to the standard of care for their lung cancer. Their imaging studies performed as part of standard of care every 3-4 months and their vital status will be periodically monitored for 3 years following treatment for the progression free survival and overall survival analyses.

	Day 0 **BH ^{18}F-FDG PET/CT**	**^{18}F-FMISO1** (within 14 +/- 5 days after the baseline ^{18}F-FDG scan, and before starting therapy)	**Mid Treatment Scans**		**Follow up**
			^{18}F-FMISO2 Within occur two weeks +/- 4 days post initiation of therapy	**^{18}F-FDG** (FDG: 3 to 4 weeks +/- 4 days post-initiation of therapy	
Informed consent	X				
Review of your history and medication	X				
Physical exam	X				
Vital signs	X	X			
Standard clinical ^{18}F-FDG PET/CT scan	X		X		
^{18}F-FMISO tracer injection		X[1]	X[1]	X	
Research PET scans	X	X	X	X	
Research blood draws		X	X		
Review of medical record for PFS and OS					X
Standard clinical CT of the chest					X[3]
Vital signs and Toxicity assessment[2]		X	X		

Table 1. Group 1: FMISO 2 Mid-Treatment Group Study Outline

	Day 0 **^{18}F-FDG PET/CT**	**^{18}F-FMISO1** (within 14 +/- 5 days after the baseline ^{18}F-FDG scan, and before starting therapy)	**Simultaneous ^{18}F-FDG/^{18}FMISO 2** (at least one day after the first ^{18}F-FMISO scan but before starting therapy. This must also be within 14 +/- 5 days after baseline FDG scan)	**Optional Mid Treatment** ^{18}F-FDG (3 weeks +/- 4 days after RT)	**Follow up**
Informed consent	X				
Review of your history and medication	X				
Physical exam	X				
Vital signs	X	X			
Standard clinical ^{18}F-FDG PET/CT scan	X		X		
^{18}F-FMISO tracer injection		X[1,2]	X[1,2]	X	
Research PET scans	X	X	X	X	
Research blood draws		X	X	X	
Review of medical record for PFS and OS					X
Standard clinical CT of the chest					X[3]
Vital signs and Toxicity assessment[2]		X			

Table 2. Group 2: Simultaneous FDG and FMISO group study outline

1. The ^{18}F-FMISO and the simultaneous ^{18}F-FDG/^{18}F-FMISO studies on each day will be performed in up to three separate imaging sessions, as was described earlier.
2. Vital signs and toxicity assessments will be performed immediately after each FMISO scan session. Additionally, approximately 24 hours (or on the next business day) after the completion of each scan session, a toxicity assessment will be completed via a telephone followup.
3. CT of the chest will be performed every 3 to 4 months from the completion of treatment for 3 years as per standard clinical care.

11.0 TOXICITIES/SIDE EFFECTS

No acute side effects are expected as a result of this study. However, in the unlikely event that an adverse reaction to either radiopharmaceutical occurs, the results must be documented and reported by the Principal Investigator to both the Institutional Review Board, and the Investigative New Drug Committee.

To ensure patient safety, vital signs and toxicity assessments will be performed immediately after each scan session. Additionally, approximately 24 hours (or on the next business day) after the completion of each scan session, a toxicity assessment will be completed via a telephone followup.

The risks of this study include exposure to unnecessary radiation. This risk will be clearly outlined in the informed consent.

Adverse Events will be graded using the NCI Common Terminology Criteria for ADverse Events-Version 4.0.

Information about both diagnostic agents, ^{18}F-FDG and FMISO, and the corresponding dosimetry tables are summarized below.

11.1 ^{18}F-FDG PET Scan

11.1.1 ^{18}F-FDG PET Schedule

^{18}F-FDG is an FDA approved radiotracer. In patients who are receiving radiation and agree to participate in this protocol, one additional ^{18}F-FDG PET scan will be obtained mid-treatment (as described in section 1.0) to assess response to therapy. This follow up FDG scan is investigational. Besides, in the baseline FDG PET/CT, which is standard of care, additional two one PET/CT FOV over the lesion will be acquired following the clinical scan. This additional FOV is investigational and will be acquired first in FB and then in BH (same as for the investigational follow up FDG PET/CT study). The CT components will be acquired in cine mode and then BH respectively.

Only patients in Group 1 will participate in BH scans.

11.1.2 ^{18}F-FDG Production

All ^{18}F-FDG doses will be purchased from IBA.

11.1.3 Dosimetry Estimates for ^{18}F-FDG

Table 3 below summarizes normal organ doses due to ^{18}F- FDG administration.

	Absorbed Doses		
	Follow Up FDG PET/CT		
Target Organ	Median Dose (rad/mCi)	0.903 rad(*) + Dose (rad) per 12mCi FDG	0.903 rad(*) + 0.837 rad(**) Dose (rad) per 12mCi FDG
Adrenals	0.052	0.624	0.624
Bone Surfaces	0.037	0.444	0.444
Brain	0.17	2.04	2.04
Gall Bladder Wall	0.088	1.056	1.056
Heart Wall	0.25	3.903	4.74
Kidneys	0.078	0.936	0.936
Large Intestine - Lower Wall	0.059	0.708	0.708
Large Intestine - Upeer Wall	0.048	0.576	0.576
Lens of Eye	0.041	0.492	0.492
Liver	0.088	1.056	1.056
Lungs	0.0028	0.9366	1.7736
Muscle / Other Tissue	0.041	0.492	0.492
Pancreas	0.052	0.624	0.624
Red Marrow	0.041	1.395	2.232
Small Intestine	0.048	0.576	0.576
Stomach Wall	0.044	0.528	0.528
Testes	0.056	0.672	0.672
Thyroid	0.012	0.144	0.144
Total Body	0.043	0.516	0.516
Urinary Bladdr Wall			
45 min Voiding Interval	0.165	1.98	1.98
1 hr Voiding Interval	0.22	2.64	2.64
1.5 hrs Voiding Interval	0.34	4.08	4.08
2 hr Voiding Interval	0.44	5.28	5.28
Effective Dose Equivalent (rem)	0.1	1.46187	1.7046

(*) Cumulative CT dose from FB-CT (0.066 rad), BH-CT (0.066 rad), and 4D-CT (0.771 rad) (Total = 0.903 rad)
(**) Cumulative CT dose from BH-CT (0.066 rad) and 4D-CT (0.771 rad) (Total = 0.837 rad)

(1) FDG Package Insert, Eastern Isotopes, Inc, Asbnun, VA, 1998.
(2) Wu et al. Eur J Nucl Mol Imaging 31:38-43, 2004.

Table 3.

The organ receiving highest radiation dose from the investigational ^{18}F-FDG scan is the heart wall (3.0 rad). Additional doses of 0.066 rad from the FB CT, 0.771 rad from one 4D-CT scans (avg CT) and 0.066 rad from a BH-CT will be delivered to the patient. The total dose to the heart wall from the investigational ^{18}F-FDG scan is 4.74 rad.

11.2 ^{18}F-FMISO PET Scan

11.2.1 ^{18}F-FMISO PET Schedule

^{18}F-FMISO is a radiotracer which MSKCC holds an approved IND. In patients who agree to participate in this protocol, two ^{18}F-FMISO PET Scans will be obtained within 5 days, at least 1 day after the baseline ^{18}F-FDG-PET that is required as part of pretreatment enrollment criteria.

11.2.2 ^{18}F-FMISO Production

F18-fluoride is produced by the Memorial Sloan-Kettering Cancer Center cyclotron by proton irradiation of an enriched O-18 water target in a small-volume titanium chamber. ^{18}F- FMISO is prepared at an approximate specific activity of 2.5x10^{7}MBq/mmol at production time. Patients will be injected with a maximum of 10 +/- 10% mCi of ^{18}F-FMISO on each of the 2 ^{18}F-FMISO scan days.

11.2.3 Dosimetry Estimates for ^{18}F-FMISO

Bio-distribution data has been obtained for 25patients at the University of Washington, and dosimetry was performed. Table 4 below summarizes normal organ doses due to ^{18}F- FMISO administration.

F18-FMISO Patient Dosimetry

	Absorbed Doses		
Target Organ	Median Dose (rad/mCi)	2.51 rad(*) + Dose (rad) per 10mCi FMISO	2x2.51 rad(*) + Dose (rad) per 2x10mCi FMISO
Adrenals	0.0614	0.614	1.228
Brain	0.0318	0.318	0.636
Breasts	0.0455	0.455	0.91
Heart Wall	0.0685	3.195	6.39
Stomach	0.0466	0.466	0.932
Kidney	0.0581	0.581	1.162
Liver	0.0677	0.677	1.354
Lungs	0.0366	2.876	5.752
Muscle	0.0525	0.525	1.05
Ovaries	0.0651	0.651	1.302
Red Marrow	0.0403	2.913	5.826
Spleen	0.0603	0.603	1.206
Thyroid	0.0559	0.559	1.118
Eye Lens	0.057	0.57	1.14
Total Body	0.0466	0.466	0.932
Urinary Bladder Wall			
45 min Voiding Interval	0.0291	0.291	0.582
1 hr Voiding Interval	0.0389	0.389	0.778
1.5 hrs Voiding Interval	0.0583	0.583	1.166
2 hr Voiding Interval	0.0777	0.777	1.554
Uterus	0.0677	0.677	1.354
Effective Dose Equivalent (rem)	0.0481	0.481	0.962

Table 4.

The organ receiving highest radiation dose from the two ^{18}F-FMISO scans is the heart wall (2x0.685 rad). Additional doses from 6 BH-CT scans (3 BH-CT per ^{18}F-FMISO study) of 0.396 rad (6 x 0.066 rad) , and six 4D-CT scans (avg CT) (three 4D-CT per ^{18}F-FMISO study) of 4.626 rad (6 x 0.771 rad) for a total of 2.51 rad per ^{18}F-FMISO study or 5.02 rad for both ^{18}F-

FMISO studies, will be delivered to the patient bringing the total radiation dose to the heart wall to 6.39 rad .

11.2.4 Dosimetry Estimates for simultaneous ^{18}F-FMISO/^{18}F-FDG

Based on the dosimetry data of tables 1 and 2, dosimetry was performed. Table 5 below summarizes normal organ doses due to simultaneous ^{18}F-FMISO/^{18}F-FDG administration.

Absorbed Doses			
Dual FDG/FMISO			
Target Organ	**Dose (rad) per 8mCi FDG**	**Dose (rad) per 8mCi FMISO**	**0.198rad + 2.313 rad + Dose (rad) per 8mCi FMISO + per 8mCi FDG**
Adrenals	0.416	0.491	0.907
Bone Surfaces	0.296	0.228	0.524
Brain	1.36	0.254	1.614
Gall Bladder Wall	0.704	0.438	1.142
Heart Wall	2	0.548	5.059
Kidneys	0.624	0.465	1.089
Large Intestine - Lower Wall	0.472	0.423	0.895
Large Intestine - Upeer Wall	0.384	0.414	0.798
Lens of Eye	0.328	0.456	0.784
Liver	0.704	0.542	1.246
Lungs	0.0224	0.293	2.826
Muscle / Other Tissue	0.328	0.420	0.748
Pancreas	0.416	0.530	0.946
Red Marrow	0.328	0.322	3.161
Small Intestine	0.384	0.390	0.774
Stomach Wall	0.352	0.373	0.725
Testes	0.448	0.432	0.880
Thyroid	0.096	0.447	0.543
Total Body	0.344	0.373	0.717
Urinary Bladdr Wall			
45 min Voiding Interval	1.32	0.233	1.553
1 hr Voiding Interval	1.76	0.311	2.071
1.5 hrs Voiding Interval	2.72	0.466	3.186
2 hr Voiding Interval	3.52	0.622	4.142
Effective Dose Equivalent (rem)	0.8	0.385	1.185

(1) FDG Package Insert, Eastern Isotopes, Inc, Asbnun, VA, 1998.
(2) Wu et al. Eur J Nucl Mol Imaging 31:38-43, 2004.

Table 5.

The organ receiving highest radiation dose from the combined FMISO/FDG scan is the heart wall (2.548 rad). Additional doses from 3 BH-CT scans (3 BH-CT per ^{18}F-FMISO study) of 0.198 rad (3 x

0.066 rad) , and three 4D-CT scans (avg CT) (three 4D-CT per ^{18}F-FMISO study) of 2.313 rad (3 x 0.771 rad), bringing the total dose to the heart to 5.059 rad per FMISO/FDG study.

11.2.5 Total Doses from All Studies

Based on the dosimetry data of tables 1 and 2, dosimetry was performed. Table 6 below summarizes the total normal organ doses from the FDG PET/CT, 2xFMISO PET/CT, and combined FMISO/FDG PET/CT.

Absorbed Doses				
Total Dose from All FDG and FMISO studies (including the corresponding CT-BH's amd 4DCT's)				
Target Organ	**0.903 rad(*) + 0.837 rad(**) Dose (rad) per 12mCi FDG**	**2x2.51 rad(*) + Dose (rad) per 2x10mCi FMISO**	**0.198rad + 2.313 rad + Dose (rad) per 8mCi FMISO + per 8mCi FDG**	**Total Dose**
Adrenals	0.624	1.228	0.907	2.759
Bone Surfaces	0.444	0.57	0.524	1.538
Brain	2.04	0.636	1.614	4.290
Gall Bladder Wall	1.056	1.095	1.142	3.293
Heart Wall	4.74	6.39	5.059	16.189
Kidneys	0.936	1.162	1.089	3.187
Large Intestine - Lower Wall	0.708	1.0575	0.895	2.661
Large Intestine - Upeer Wall	0.576	1.035	0.798	2.409
Lens of Eye	0.492	1.14	0.784	2.416
Liver	1.056	1.354	1.246	3.656
Lungs	1.7736	5.752	2.826	10.352
Muscle / Other Tissue	0.492	1.05	0.748	2.290
Pancreas	0.624	1.325	0.946	2.895
Red Marrow	2.232	5.826	3.161	11.219
Small Intestine	0.576	0.975	0.774	2.325
Stomach Wall	0.528	0.932	0.725	2.185
Testes	0.672	1.08	0.880	2.632
Thyroid	0.144	1.118	0.543	1.805
Total Body	0.516	0.932	0.717	2.165
Urinary Bladdr Wall				
45 min Voiding Interval	1.98	0.582	1.553	4.115
1 hr Voiding Interval	2.64	0.778	2.071	5.489
1.5 hrs Voiding Interval	4.08	1.166	3.186	8.432
2 hr Voiding Interval	5.28	1.554	4.142	10.976
Effective Dose Equivalent (rem)	1.2	0.962	1.185	3.347

(1) FDG Package Insert, Eastern Isotopes, Inc, Asbnun, VA, 1998.
(2) Wu et al. Eur J Nucl Mol Imaging 31:38-43, 2004.

Table 6.

The organ receiving the highest radiation dose in the case of the five patients that will undergo the combined FMISO/FDG study is the heart at 16.189 rad. This is based on the doses from the mid-treatment FDG scan, the baseline and follow up FMISO scan, the combined FMISO/FDG scan, and all the corresponding CT's.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

There are two primary goals for this study; first, to assess the reproducibility of kinetic analysis of dynamic ^{18}F-FMISO PET images, in both BH and FB data sets, and second, to assess the prognostic value of hypoxia, as measured with ^{18}F-FMISO PET, with OS and PFS in NSCLC. As explained above, the presence and extent of tumor hypoxia will be measured by means of kinetic analysis of dynamic ^{18}F-FMISO PET images. Kinetic analysis parameters may be susceptible to breathing-induced motion artifacts due to patient respiration. Hence, the correlation of outcome to both the presence and extent of tumor hypoxia may be inaccurate .We will therefore conduct analyses based on BH- and FB- PET datasets, and then compare the results in order to assess the effect breathing on these parameters. This exploratory objective of tumor hypoxia correlation to clinical endpoints is dependent on time to tumor progression and death. We will follow up with these patients up to a maximum of three years. The table below summarizes the milestones of this research project.

Likewise, the predictive value of FDG PET may also be suspect due to breathing motion artifacts. In light of the discussion above, therefore, the secondary aim is to compare the predictive value of FDG PET when the data are acquired in BH versus in FB PET.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient develops unacceptable toxicity he/she will be removed from study. An unacceptable toxicity will be defined by a grade III/IV toxicity requiring hospitalization as per CTCAE v4.0

If at any time the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (i.e., a change in diagnosis), the patient will be removed from the study.

Patients who are withdrawn from the study before completing all protocol required scans will be replaced to ensure there are 25 evaluable patients.

14.0 BIOSTATISTICS

This study will enroll 25 patients with non-small cell lung cancer (NSCLC) who will undergo treatment with definitive conventionally fractionated radiation therapy (RT), neoadjuvant chemotherapy, or chemo-RT. In addition to standard of care PET/CT scans, they will also be scanned twice at baseline (pre-treatment) with experimental ^{18}F-FMISO scans.

Since some patients will have multiple lesions some of the statistical analyses will be lesion-based and some will be patient-based. This is explained in detail within each analysis but primarily, reproducibility analyses will be lesion-based and analysis of predictive values will be patient-based. Presence and extent of hypoxia will be analyzed twice, one lesion-based and the other patient-based. One of the primary objectives is to evaluate the reproducibility of kinetic analysis in serial, BH and Free-Breathing (FB), dynamic ^{18}F-FMISO PET images. Hypoxia is measured by k3, the trapping rate (see section 7.3). This will be analyzed both as a binary and a continuous variable: if any of the voxels

inside the tumor has a k3>0.1 the tumor is defined to be hypoxic while its extent will be defined by the fraction of hypoxic volume which is the fraction of tumor volume with k3>0.1. Reproducibility will be evaluated using Cohen's kappa for presence of hypoxia and concordance correlation coefficient for the extent of hypoxia. This will be a lesion-based analysis and multiple observations per patient will be taken into account using a variance inflation factor estimated from the intraclass correlation coefficient.

Another primary objective is to compare the presence and extent of hypoxia with the clinical outcome (see section 7.3 and above for the definition of hypoxia). Previous studies showed comparable outcomes for stage IIIA (which is the majority treated) when following either of the two treatment arms considered in this study (*51, 52*).

Therefore, data from both groups of patients will be analyzed together. Historical data suggests 38% of patients will be free of recurrence at 3 years (*53*), which provides us with approximately 80% power to detect a hazard ratio of 3.0 between groups of low and high change. This calculation is based on a log-rank test and assumes that extent of hypoxia is dichotomized at observed median resulting in equal group sizes and maximal power. This is for planning purposes only. We will use Cox regression with extent of hypoxia as the covariate in two different ways: (1) lesion-based analysis with an estimating equations to account for multiple observations per patient; (2) patient-based where an aggregate measure of extent of hypoxia (sum of the fraction of tumor volumes with k3>0.1 across all lesions) over all lesions within a patient) will be used as a covariate. In addition, a lesion and patient-based analyses for presence of hypoxia will also be considered where, for the patient-based analysis, the aggregate measure will be defined as presence of hypoxia in at least one of the lesions.

In an exploratory analysis to address the secondary objective of assessing the predictive value of FDG PET/CT in a group of twenty five lung cancer patients undergoing radiotherapy or concurrent chemoradiotherapy, we will use the concordance probability estimate from a proportional hazars regression model with SUV as the predictor for the outcomes of survival and progression-free survival. Time of origin will be the start time of therapy (neoadjuvant therapy, if applicable, concurrent chemoradiation or radiation alone otherwise). We will use these estimates to preliminarily determine whether BH PET/CT provides greater predictive capability than Free-Breathing (FB) PET/CT. Since these analyses are exploratory findings will be interpreted as hypothesis-generating.

We expect to accrue one patient a month for each of the two cohorts.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record. Study personnel will record clinical data in each patient's source documents (i.e., the patient's medical record). The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure, the investigator will maintain all source documents, study-related documents, and the data stored in the database used for data collection. Data will be entered throughout the duration of the trial as patients are enrolled

16.1 Quality Assurance

Eligibility of patients will be verified with the principal investigator. Only the designated investigators can obtain informed consent.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board (see section 16.2).

During the protocol development and review process, each protocol will be assessed for the level of risk and the degree of required monitoring. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) is reviewed and monitoring procedures are established at the time of protocol activation.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: *http://cancertrials.nci.nih.gov/researchers/dsm/index.html*. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*.

17.0 PROTECTION OF HUMAN SUBJECTS

There are no foreseen additional risks to the patients from this study.

Risks of Study Participation: Patients in this study will be receiving current standard of care for their specific disease site.

Financial Costs to Patients: All diagnostic and therapeutic interventions except for the FMISO-PET scans and the mid-treatment FDG PET/CT are part of the current routine care of patients/subjects eligible for this study and. A research grant will cover the cost of the FMISO-PET scans and the tracer, blood PK samplings and the mid-treatment FDG PET/CT. There are no additional financial costs or burden to the patient beyond the charges routinely incurred as part of standard medical care.

Patient Confidentiality: Patient/subject privacy and confidentiality will be maintained according to MSKCC guidelines and all data derived from this study will be kept in a secure database. All data and results will be anonymously reported with regard to individual subjects.

Voluntary nature of the study: Subjects will be made aware of the voluntary nature of the study as part of the informed consent process. They will be allowed to withdraw participation at any time without the risk of alteration in the quality of their medical care.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research

Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.2.1

Any additional SAE reporting information required by the sponsor or drug supplier should be included in this section.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.

5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

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20.0 APPENDICES

Not applicable.