RTOG 1106 (A3) Section 6: Radiation Therapy

6.0 RADIATION THERAPY/FUNCTIONAL IMAGING (8/19/13)

NOTE: Institutions must complete the pre-registration credentialing requirements in Sections 5.1 through 5.5 before registering patients on this study.

In addition to the requirement that each institution complete a Benchmark credentialing case (see Sections 5.2.2, 5.3.2 and 5.4.1), the first case of the experimental arm (Arm 2) from each institution will be submitted for Pre-treatment Review. Subsequent patients cannot be enrolled until this first case has successfully passed the pre-treatment review process. See Section 5.4.3 for more details.

The Principal Investigator, Feng-Ming (Spring) Kong, MD and the Medical Physics Co-Chairs, Randall Ten Haken, PhD, Ying Xiao, PhD, and/or Martha Matuszak, PhD, will perform these pre-treatment (rapid) reviews. Institutions should allow 3 business days from the time complete and relevant information is received by RTOG until approval for the pre-treatment review case is returned to the institution via e-mail. It is incumbent upon the institution to send the complete plan information needed for pre-treatment review as quickly as possible so that the strict timelines required for this study can be met. In situations in which the reviewers identify treatment plan changes, every effort should be made to submit requested information as quickly as possible. See Section 12.2 for submission details for the pre-treatment review process. Once approved, RTOG RTQA will notify the institution by e-mail.

Sites will direct questions to Jennifer Presley, RTOG Lung Team Dosimetrist, jpresley@acr.org or call the RTQA Main Number at (215) 574- 3219 for assistance.

Protocol treatment must begin within 2 weeks after registration.

Table 6.0: RT Plan and PET/CT Scan Flowchart (8/19/13)

<table>
<tr><th colspan="2">Eligible stage III NSCLC, Protocol Registration</th></tr>
<tr><td colspan="2">1. Repeat FDG-PET/CT if it was performed > 4 weeks previously or if it was not adequate for the RT plan (e.g. patient not in treatment position or on flat tabletop); see Section 6.14.3 for FDG-PET/CT imaging requirements
2. FMISO-PET/CT only in selected centers; see Section 6.10.3 for F-MISO-PET/CT imaging requirements.</td></tr>
<tr><td colspan="2">Stratified Randomization:
Stage, Primary Tumor Size and Histology)
All patients will receive 30 treatments</td></tr>
<tr><td>Arm 1: Control Arm
2 Gy per fraction for all patients

Uniform dose prescription in all patients and uniform dose to all PTVs throughout the RT course</td><td>Arm 2: Experimental Arm
2.2-3.8 Gy per fraction, individualized to 20 Gy MLD and adapted to residual tumor on the during-RT FDG-PET/CT

First Phase:
Dose per fraction will be 2.2 Gy per fraction for 21 fractions.</td></tr>
<tr><td>Perform FDG-PET/CT at 39.6 Gy (between fractions 18 and 19) for treatment response assessment only</td><td>Perform PET-CT and CT resimulation at 39.60 Gy (between fractions 18 and 19) for treatment response assessment and adaptive plan.</td></tr>
</table>

Continue treatment of the initial plan at 2 Gy per fraction without changes or adaptions	**Adaptive Phase:** Adaptive plan treated at 2.2-3.8 Gy per fraction for the final 9 fractions. Dose per fraction individualized to maximize dose to residual PET tumor subject to MLD ≤ 20 Gy and other normal tissue limits (Table 6.5.2)
To a total dose of 60 Gy	To a **maximum physical dose or 80.4 Gy** (first phase plus adaptive boost)

6.1 Dose Specifications (8/19/13)

6.1.1 Arm 1 (control arm)

Patients on Arm 1 will receive a single prescription of 60 Gy in 30 fractions in 6 weeks, with RT given once daily, 5 days a week. There are no field reductions or adaptation. All fields must be treated daily. On days when chemotherapy is given, it will be administered prior to RT.

For patients with MLD > 20 Gy at 60 Gy prescriptions, RT dose will be not be changed. This is based on the results of RTOG 7301. This study showed that 60 Gy in 6 weeks is a safe prescription without 3D consideration of doses to OARs and generates superior local control compared to lower doses (Perez 1983).

If a patient develops disease progression on the during-RT FDG-PET/CT scan, radiation therapy per protocol description will stop if the progression is 1 cm outside of the original PTV. The remaining treatment of this patient will be per discretion of the treating physician. Pathological proof is required for such a change in treatment; otherwise, the patient should continue protocol treatment per the initial plan

6.1.2 Arm 2 (experimental arm)

Patients on Arm 2 will receive an individualized RT prescription of total MLD $\leq$ 20 Gy, up to a total dose of 80.4 Gy given in 30 daily fractions in 6 weeks. The RT plan will be adapted to target the tumor on the during-treatment FDG-PET/CT obtained after an initial dose of 39.6 Gy (after 18 fractions)has been delivered. The adaptive RT will start after an initial dose of 46.2 Gy has been delivered. .

Like the control arm, all planned fields must be treated daily during the planned course of treatment. This applies to the initial treatment plan used to deliver the dose up to 46.2 Gy as well as the “adaptive” treatment plan used to complete dose delivery. On days when chemotherapy is given, it must be administered prior to RT.

For Arm 2, a minimum dose of 66 Gy will be given in total to those patients with MLD > 20 Gy (46.2 Gy + 19.8 Gy). With expected reduction of PTVs in most cases, through the use of this adaptive plan, most patients will have an opportunity to have PTV doses escalated (greater than 66 Gy in those with MLD ≤ 20 Gy) without increasing the doses to organs at risk, The maximum dose is 80.4 Gy. In all patients, the radiation is planned for a final composite MLD of 20 Gy or less if limited by doses to other OARs, and the pre-RT PTV, pre-RT CTCTV (CT1CTV), and during-RT CTPTV (CT2PTV) will receive at least 50, 60, and 70 Gy (or the prescription dose if the final prescription dose is less than 70 Gy), respectively. Doses to the other organs at risk are discussed in Section 6.5 below.

If a patient develops disease progression on the during-RT FDG-PET/CT scan, radiation therapy per protocol description will stop if the progression is 1 cm outside of the original PTV. The remaining treatment will be per the discretion of the treating physician. Pathological proof is required for such a change in treatment; otherwise, the patient should continue protocol treatment.

To make the adaptive plan possible, the patient must have the during-RT FDG-PET/CT scan and resimulation performed according to the timeline in Table 6.1.2 below:

Table 6.1.2: Timeframe for Acquiring the During-RT FDG-PET/CT Scan

Treatment Arms	***# of fractions before the during-RT PET/CT***	***Variation Acceptable if # of fractions before the during-RT PET/CT***	***Deviation Unacceptable if # of fractions before the during-RT PET/CT***
Arm 1 and Arm 2	18	17-19	≤ 16 or ≥ 20

6.1.3 Dose Calculations

All radiation doses will be calculated with inhomogeneity corrections that take into account the density differences within the irradiated volume (i.e. air in the lung and bone).

For purposes of this study, the acceptable heterogeneity correction dose calculation algorithms can be found on the RPC web site at http://rpc.mdanderson.org/rpc. Click on the highlighted box in the upper right corner of the web site. Call the RPC at 713-745-8989 with any questions regarding this. Non-validated dose calculation algorithms (i.e. Clarkson or pencil beam) will not be allowed for this study.

For free-breathing treatment, dose calculations should be performed on an untagged or average scan generated from 4D CT data or on a CT scan obtained at normal voluntary exhale when 4D CT is not available, and motion assessment is achieved through 2 phase CT scans. For breathing controlled treatments, dose calculations should be performed on the CT taken at the motion controlled state to be used for treatment. If oral and/or IV contrast is used and significant contrast is noted within the dose calculation volume, density overrides should be performed for dose calculations. See Section 6.3.2 for more details as to which CT simulation dataset should be listed as the primary dataset.

6.2 Technical Factors (12/5/12)

Megavoltage equipment is required with effective photon energies of 6-10 MV. IMRT is allowed. If you have changed your IMRT system (e.g. to tomotherapy or VMAT), then you are required to repeat the credentialing process with an additional phantom irradiation (see Section 5.0). **IGRT is mandatory for all patients** (See Section 5.0).

Blocking: All fields must be individually shaped to minimize structures and lung not within the target volume. Divergent custom-made blocks or multi-leaf collimation will be used.

6.3 Simulation and Target Consideration (8/19/13)

6.3.1 Immobilization, Motion Assessment, Simulation, Motion Management, and Localization

Immobilization

Patients will be positioned in a stable position capable of allowing accurate reproducibility of the target position from treatment to treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be used, including using an alpha-cradle or vac-bag. Stereotactic frames that surround the patient on 3 sides and large rigid pillows (conforming to patients' external contours) may be used as indicated.

Motion Assessment and Motion Management

Special considerations must be made to account for the effect of internal organ motion (e.g. breathing) on target positioning and reproducibility. As a first step, it is required that each site quantify the specific target motions of each patient, so as to determine if management strategies are needed (motion management strategies are not needed for patients with target motion $\leq$ 5 mm). Options for motion assessment include real time fluoroscopy (using either the accelerator table when an IGRT system with fluoroscopy capability is available or a conventional simulator with fluoroscopy), or 4-D CT scanning. Motion should be controlled for any RT treatment in patients with tumor motion greater than > 1.5 cm. Abdominal compression is an effective method for reducing target motion so that the GTV stays within the set margins for this protocol (< 5 mm). However, institutions selecting abdominal compression for motion management should not use this method for patients for whom the compression does not effectively dampen the respiratory motion to within 5 mm.

Centers credentialed for RTOG SBRT lung trials are automatically approved for motion management for this trial. However, the motion management credentialing process must be repeated when an institution's motion management technique has changed. For example, if the method has changed from abdominal compression to linear accelerator gating, re-credentialing will be required.

Simulation

Simulation CT scans of the chest will cover whole lung with an adequate margin for generation of digitally reconstructed radiographs (DRRs) and treatment planning with non-coplanar fields, normally from C2-3 to L3-4. Scans will be performed either under free breathing with multiple-phased 4D CT scans at a fixed breathing phase for motion management, or using 2 phases with breath held at the end of voluntary inhale, at the end of voluntary exhale. Patients should be instructed to be in normal free breathing at the time of the initial tumor motion assessment. Deep inspiration or expiration breath hold is not allowed for initial tumor motion assessment as such assessments generally overestimate free breathing tumor motion. For accurate target delineation, and oral contrast should be used for all patients whenever possible. For 4-D CT scanning, a separate CT scan performed at the end of the natural exhale can be performed for contrast. Note that if contrast produces clinically relevant density changes or artifacts in the dose calculation volume, density overrides should be performed to obtain accurate dose calculations (see Section 6.1.4 for details regarding acceptable scans for dose calculations).

For Arm 2 patients, an adaptive CT-resimulation should be performed for contouring of the CT2GTV. Patient positioning and immobilization should match the technique used for the initial CT-simulation. The same motion management technique should be applied as was chosen for the initial plan (for example, if a 4DCT was used for contouring the CT1GTV in the initial plan, a 4DCT should be repeated and used for contouring of the CT2GTV for the adaptive plan).

Localization

Patients will undergo a 2D or 3D IGRT procedure or in-room CT study immediately before treatment to ensure proper alignment of the geometric center (i.e., isocenter) of the simulated fields.

6.3.2 Radiation Target Volume Definition

Target volumes should be defined according to Table 6.3.2 (below):

Table 6.3.2: Target Contours

Structure	Description	Contouring Instructions	Dataset Instructions
Required for Arm 1 and Initial Plan of Arm 2			
CT1GTV	CT1 Primary and Nodal Gross Tumor Volume	Drawn by Physician	Defined on CT1

PET1MTV	PET1 Primary and Nodal Metabolic Tumor Volumes	Autotracked at threshold of 1.5 x mean intensity of 1 cc aorta volume	Defined on PET1; Transferred to CT1 for contour review.
PreGTV	GTV for Arm 1 and Initial Plan of Arm 2	Composite of CT1GTV and PET1MTV	Created on CT1
PreCTV	CTV for Arm 1 and Initial Plan of Arm 2	0.5 cm expansion from PreGTV	Created on CT1
PrePTV	PTV for Arm 1 and Initial Plan of Arm 2	0.5 cm expansion from PreCTV	Created on CT1
Required for Adaptive Plan of Arm 2			
CT2GTV	CT2 Primary and Nodal Gross Tumor Volume; Secondary GTV for Adaptive Plan of Arm 2	Drawn by Physician	Defined on CT2; Copied to CT1 for dose evaluation
PET2MTV	PET2 Primary and Nodal Metabolic Tumor Volumes	Autotracked at threshold of 1.5 x mean intensity of 1 cc aorta volume	Defined on PET2; Transferred to CT1 for contour review.
CT2PTV	PTV based on CT2GTV; Secondary PTV for the Adaptive Plan of Arm 2	1 cm expansion of CT2GTV	Created on CT1 for dose evaluation (note: source CT2GTV is on registered CT2 dataset)
DurGTV	Main GTV for Adaptive Plan of Arm 2	Equals PET2MTV	Created on CT1 (note: source PET2MTV on registered PET2 dataset)
DurPTV	Main PTV for Adaptive Plan of Arm 2	0.5 cm expansion from DurGTV (note: there is no DurCTV)	Created on CT1

Target Volume (Arm 1 Plan and the Initial Plan for Arm 2)

The initial planning target volume (Pre-PTV) should be based on composite GTVs from pretreatment simulation CTs with targets attached or registered to the primary imaging dataset (CT1) and the pretreatment FDG-PET/CT (PET1). The primary dataset, CT1, will be defined as follows:

- For free-breathing treatment with a 4D CT simulation: CT1 = Average CT generated from 4D CT;
- For free-breathing treatment without 4D CT simulation: CT1 = Normal exhale CT scan;
- For motion controlled treatments: CT1 = CT scan at the motion controlled state.

CT1GTV will be a composite volume of the primary tumor mass and nodal diseases . Contrast is recommended to aid in accurate GTV delineation. Guidelines for contouring GTVs are as follows:

- For free-breathing treatment with a 4DCT simulation, the GTVs will be composite volumes from CT scans throughout the breathing phases, with inclusion of target motion.
- For free-breathing treatment without 4DCT simulation, the GTVs will be composite volumes from inhale and exhale CT scans, with inclusion of target motion. For motion controlled treatments, the GTVs should be generated from a CT scan at the motion controlled state.

Regarding lymph nodes, the CT1GTV should include

1. any hilar or mediastinal lymph nodes≥ 1 cm in short axis on composite v olumes of 4D CT or both exhale and inhale CT;
2. any nodes with abnormal findings detected on bronchoscopy and/or mediastinoscopy;
3. any visible nodes that are growing or with abnormal structures;
4. 2 more nodes clustered in the high risk nodal stations
5. any visible nodes at the 1st echelon or with 1cm proximity to the primary tumor, if applicable.

The primary tumor should be contoured on CT images under a standard lung window/level for its lung borders and under a mediastinal window/level for the borders adjacent to mediastinum. The nodes should be drawn under the window and level setting of mediastinum. In cases with extensive atelectasis and/or pneumonia where tumor margins are obscure, volumes are left to the judgment of the treating radiation oncologist.

The PET Metabolic Target Volume (PET1MTV) of both the primary tumor and nodal disease on PET/CT scan also should be contoured. The PET intensity of a 1 cc volume in the aortic arch should be contoured and used for normalization. Any primary or nodal disease on PET with an intensity greater than or equal to 1.5 times the mean of the aortic arch intensity should be included in the MTV.

PET1MTV plusCT1GTV makes the total PreGTV. The initial clinical target volume (PreCTV) will consist of the PreGTV and approximately a 0.5 cm margin for microscopic extension. Radiographically uninvolved supraclavicular nodes, para-tracheal nodes, and subcarinal nodes will not be intentionally included in the PreCTV. The PrePTV will consist of the PreCTV plus a minimal 0.5 cm margin for set-up error plus an individualized margin for target motion if the motion is not controlled or the Pre-GTV did not include the target motion.

Target Volume for the Arm 2 Adaptive Treatment

The primary PTV for the adaptive plan will be the DurPTV, which is defined based on the during-RT PET/CT study and consists of the PET2MTV plus at least a 0.5 cm expansion. The PET2MTV should be outlined on the PET/CT scan acquired at fx 18-19 during the course of RT. The PET2MTV should be auto-contoured using the same normalization method (Threshold = 1.5 x 1 cc mean intensity of aortic arch) as was used to define the PET1MTV.

The secondary PTV for the adaptive plan will be the CT2PTV which is defined on a resimulation CT, using the same motion management technique employed in the initial plan (for example, if 4DCT was used for the initial simulation for a free-breathing patient, the 4DCT should be repeated for the purpose of adaptive contouring-see Section 6.3.1). The CT2PTV will be a minimum 1.0 cm expansion of the CT2GTV (**Note**: There is no CT2CTV). The adaptive dataset, CT2, will be defined as follows:

- For free-breathing treatment with a 4DCT simulation: CT2 = Average CT generated from 4DCT;
- For free-breathing treatment without 4DCT simulation: CT2 = Normal exhale CT scan;
- For motion controlled treatments: CT2 = CT scan at the motion controlled state.

The adaptive plan is designed in a way that DurPTV will be given as high dose as possible, respecting the MLD limit of 20 Gy and the dose constraints of other normal tissues limited by a total prescription dose of 80.4 Gy. Target dose requirements are provided in Table 6.4.4. Normal tissue doses are discussed in Section 6.5 below.

6.4 Treatment Planning (8/19/13)

6.4.1 For protocol treatment, all patients will undergo CT and PET-based treatment planning. An FDG-PET/CT scan with the patient in the treatment position on a flat palette imaging couch is required pre- and during-treatment for contouring. FDG-PET/CT scans must be performed on

ACRIN credentialed scanners. GTV/MTV, CTV margin, and PTV margin are as described in Sections 6.3.2. The treatment technique and number of fields must be optimized individually. Functional image of normal tissue, such as ventilation perfusion single proton emission tomography of lungs, is allowed to guide plan optimization providing that the physical doses to tumor target and dose limits of OARs are satisfied for this study. DVHs will be used to predict the potential for normal tissue damage and will also provide objective criteria for the selection of an appropriate treatment plan. Suitable treatment plans will be those that minimize MLD while maintaining dose to other critical organs at risk (OARs) below specified limits and providing acceptable target volume coverage. With the tumor and critical organ constraints described in further detail below, the goal of the treatment planner will be to develop a plan that provides the lowest possible doses to lung and other OARs and thus, the highest dose ratio of tumor over OARs.

Dose calculations should be performed on the primary dataset, CT1, as defined in Section 6.3.2.

6.4.2 *Arm 1:* The RT plan of Arm 1 is 60 Gy, with at least 95% of the PrePTV covered by this dose. The normal tissue constraints in Table 6.5.2 are the top priority, with the exception of the MLD. All patients in Arm 1 should receive 60 Gy regardless of MLD.

6.4.3 *Arm 2:* The RT plan of Arm 2 will be individualized based on the MLD and will be adaptive. The RT plan calls for an initial treatment plan to 46.2 Gy in 2.2 Gy fractions (21 fractions) followed by an individualized boost plan that is adapted to the PET/CT scan obtained between fractions 18 and 19 during therapy (see Table 6.1.2). The prescribed dose/fraction for the boost can vary between 2.2-3.8 Gy/Fx. The prescribed dose will cover at least 95% of the PTV. The final dose is prescribed so that the total MLD is ≤ 20 Gy and doses to other organs at risk meet the limits of this trial, which are similar to those used during daily practice. **The adaptive dose/fraction should be chosen as the highest dose/fraction (up to 3.8 Gy/Fx) that allows for 95% coverage of the DurPTV and meets the normal tissue constraints listed in Table 6.5.2.** Conformal techniques including 3DCRT and IMRT are allowed.

Arm 2 Adaptive Radiation Plan Procedure

There are 6 primary sets of imaging data for adaptive planning:

a) First Simulation CT: CT1 is the primary dataset for all of the RT planning and dose calculations; CT1 should be the CT dataset used for dose calculations. This can be the average scan of 4DCT, a normal exhale CT scan or motion controlled CT scan (see Section 6.3.2).
b) Pre-treatment FDG-PET/CT: PET1, PCT1. PET1 should be used for PET1MTV determination;
c) During-RT FDG-PET-CT: PET2, PCT2. PET2 defines PET targets for adaptive plan, while PCT2 will be used as a reference anatomic scan to register PET2 to CT1;
d) During-RT simulation CT: CT2. CT2 (see Section 6.3.2) defines CTGTVs for adaptive plan.

Tumor targets are defined in Section 6.3.2. OARs must be delineated on CT1. Since only CT1 will be used for all the RT planning, there is no need to contour OARs on CT2.

Steps for Dosimetric Planning for Arm 2

1. All the imaging datasets must be registered with the CT1 dataset (i.e. the Pre-RT simulating CT scan).
2. Generate an initial plan to deliver 2.2 Gy/Fx to 46.2 Gy (21 fx).
3. Obtain resimulation CT and during-RT FDG PET/CT between fractions 18 and 19.
4. Register during-RT scans to pre-RT CT (primary dataset for dose calculations)
5. Generate an adaptive plan for the final 9 fractions of treatment that will deliver 2.2-3.8 Gy/Fx.The highest dose/fx should be chosen such that all of the normal tissue constraints are met and 95% of the DurPTV receives the prescribed dose. In addition, the CT2PTV, PreCTV, and PrePTV will receive at least 70 Gy, 60 Gy, 50 Gy, respectively. If the

prescription dose is limited to 66 Gy, then CT2PTV should receive 66 Gy (see Section 6.1.2)

6.4.4 Target Coverage

The expectation is conformal treatments, which minimize MLD and meet all normal tissue constraints. As a guideline, a conformity index (ratio of the volume of the prescription isodose surface to the PTV) of < 1.5 is desirable. For treatment plans limited by the dose to normal lung (the standard case), the prescription isodose surface should encompass at least 95% of each PTV or the lowest dose limit of OARs, if any of them is lower than the prescription dose. The minimum PTV dose to a point that is 0.03 cc must not fall below 90% of the prescription dose. The maximum dose must not exceed a value that is 110% of the prescribed dose and the hot spot must be located within the PTV. For PTVs which overlap or come near other critical OARs which would then limit the PTV dose to values lower than those allowed by the MLD, greater PTV dose heterogeneity will be allowed by relaxing the minimum dose specification in the region near the OAR. This situation is handled by the Variation Acceptable for PTV coverage as defined in Section 6.7.2.

Table 6.4.4: Dose Coverage of Target Structures (8/19/13)

Structure Name	Description	Dose covering 95% volume	Variation Acceptable***	Deviation Unacceptable
PreCTV	PreGTV+5mm	60 Gy or above	55-60 Gy	<55 Gy
PrePTV	PreCTV+5mm	50 Gy or above	45-50 Gy	<45 Gy
CT2PTV	PTV based on CT2GTV	70 Gy or above**	60-70 Gy	<60 Gy
DurPTV	PET2PTV=PET2MTV+5mm	Up to 80.4 Gy	5-10% less of desired dose*	< 10% less of desired dose*

***Based on MLD dose of 20 Gy and if the total dose prescription is > 80 Gy**

****If the prescription dose is above 70 Gy.**

*****The minimum dose within the PTV can fall below the 90% of the prescription dose but underdosing must be confined to areas of overlap with critical OARs. In those regions, the minimum dose to the PTV should be equal to the maximum allowed dose to the OAR, listed in Table 6.5.2.**

6.5 Critical Structures (8/19/13)

All the structures must be contoured consistently and dose limits to all normal structures should be strictly limited.

6.5.1 Delineations of Organs at Risk

Lung, spinal cord, esophagus, and brachial plexus should be based on the published atlas on organs at risk (Kong 2010), available on the RTOG web site. http://www.rtog.org/CoreLab/ContouringAtlases.aspx. Heart and pericardium should be based on the atlas on the RTOG web site.

6.5.2 Organs at Risk Tolerances

All of the critical organs listed below in Table 6.5.2 will be contoured into the treatment planning system when they are included in the field of irradiation. If any of the tolerance doses cannot be met, the prescription dose may be decreased heterogeneously according to these limits. For example, if a patient with a relative low MLD cannot receive high dose to mediastinal nodes due to dose limits of cord or esophagus, a plan may be generated to give higher dose to the primary, while giving less dose to the overlapping regions of the nodal PTV(s) to meet the cord or esophageal tolerance.

Table 6.5.2 (below) summarizes the dose constraints for OARs. All effort should be made to meet the “Per Protocol” criteria. In addition, it is desirable to minimize hotspots outside of the PTV and avoid unnecessary circumferential irradiation of the esophagus.

Table 6.5.2: Dose Limits for Organs at Risk for the Final Composite Plan* (8/19/13)

Structure Name	Description	Metric	Per Protocol	Variation Acceptable	Deviation Unacceptable
Lung	Lungs - PreGTV	Max Dose (Gy, 0.03 cc)	≤ 110 % Rx Dose	> 110% but ≤ 113 % Rx Dose	> 113 % Rx Dose
		Mean Dose (Gy)	≤ 20 Gy	> 20 Gy but ≤ 21 Gy	> 21 Gy
		Vol > 20 Gy (%)	≤ 35 %	>35% but ≤ 36 %	> 36 %
		Vol > 5 Gy (%)	≤ 65 %	>65% but ≤ 75 %	> 75 %
Heart	Heart/ Pericardium (see Atlas)	Max Dose (Gy, 0.03 cc)	≤ 70 Gy	> 70 Gy ≤ 75 Gy	> 75 Gy
		Mean Dose (Gy)	≤ 30 Gy	> 30 Gy but ≤ 31 Gy	> 31 Gy
		Vol > 30 Gy (%)	≤ 50 %	>50% but ≤ 55%	> 55%
		Vol > 40 Gy (%)	≤ 35 %	>35% but ≤ 40%	> 40%
Esophagus	Esophagus	Max Dose (Gy, 0.03 cc)	≤ 74 Gy	>74 Gy but ≤ 76 Gy	> 76 Gy
		Mean Dose (Gy)	≤ 34 Gy	>34 Gy but ≤ 35 Gy	> 35 Gy
Spinal Cord	Spinal Cord	Max Dose (Gy, 0.03 cc)	≤ 50 Gy	>50 Gy but ≤ 52 Gy	> 52 Gy
Brachial Plexus	Brachial Plexus	Max Dose (Gy, 0.03 cc)	≤ 63 Gy	>63 Gy but ≤ 65 Gy	> 65 Gy
NonPTV	External - PTV	Max Hotspot (1 cc)	≤ 105 % Rx Dose	> 105% but ≤ 110 % Rx Dose	> 110 % Rx Dose

6.6 Documentation Requirements (12/5/12)

6.6.1 See Section 12 for data submission requirements

6.7 Compliance Criteria (8/19/13)

6.7.1 Per Protocol: See Section 6.1 for target coverage and Section 6.4 for dose constraints for OARs.

6.7.2 Variation Acceptable

Deviations of this magnitude are not desirable, but are acceptable for treatment situations in which the target to critical structure geometry is challenging. The prescribed dose can cover as little as 90% of the PTV and still be a Variation Acceptable (see Section 6.4.4). The minimum dose within the PTV can fall below the 90% stated in Section 6.4.4, but underdosing must be confined to areas near overlap with critical structures listed in Table 6.5.2Table 6.4.4 lists the Variation Acceptable limits for all targets, and Table 6.5.2 lists the Variation Acceptable limits for normal tissues. This study mandates adjustment of the PTV dose when critical structure doses are exceeded.

The Variation Acceptable compliance criteria for the timing for obtaining the during-RT PET/CT scan are given in Table 6.1.2 above.

6.7.3 Deviation Unacceptable

Dose distributions falling in this region are not acceptable, and plan modifications should be attempted to improve results. A Deviation Unacceptable occurs if any of the Variation Acceptable dose limits stated above are exceeded.

6.7.4 Treatment Interruption Due to Delayed Adaptive RT Plan or Other Reasons*

	Per Protocol	**Variation Acceptable**	**Deviation Unacceptable**
Treatment Break (Treatment Days)	0-2 days	3-7 days	> 7 days
RT Treatment Duration	< 42 days	42-50 days	> 50 days

* Other reasons defined as a machine down, holidays, or weather delays. Toxicity-related breaks are not included.

6.8 R.T. Quality Assurance Reviews (8/19/13)

The Principal Investigator, Feng-Ming (Spring) Kong, MD and the Medical Physics Co-Chairs, Randall Ten Haken, PhD, Ying Xiao, PhD, and Martha Matuszak, PhD, will perform pre-treatment reviews of the initial and adaptive plans for the first patient enrolled on Arm 2 for each institution. Institutions should allow 3 business days for the plans for the 1st patient to be received, processed and reviewed (see Section 6.0). Revisions requested to any treatment plans will require a repeat submission and rapid review process **prior to the institution delivering any radiation treatment.** The Institution should take this review time into consideration during the planning of the adaptive phase of treatment, when there are 3 business days between obtaining the during-treatment PET-CT and simulation, planning, and the pre-treatment reviews for the adaptive plan for those patients randomized to Arm 2.

The ACRIN Co-Chair, Daniel A. Pryma, MD, may provide real time assistance for treatment planning decisions and real time target delineations, as needed.

Local control outcome will be assessed by a full review of the diagnostic imaging (CT and PET) by the ACRIN Co-Chairs, Daniel A. Pryma, MD and Barry A. Siegel, MD, and the Principal Investigator, Feng Ming (Spring) Kong, MD, PhD.

Drs. Kong, Pryma, and the Radiation Oncology Co-Chairs, Mitchell Machtay, MD and Jeffrey Bradley, MD will perform an RT Quality Assurance Review on an ongoing basis

Treatment breaks associated with delayed completion of adaptive plan will be reviewed as part of RTQA components. Table 6.7.4 provides protocol compliance definitions.

6.9 Radiation Therapy Adverse Events

Acute adverse event is defined as any side effect occurring within 90 days from the start of treatment. Late toxicity is defined as any side effect occurring after or persisting beyond 90 days from the start of treatment. Radiation pneumonitis will be evaluated for six months after the start of radiation treatment. **Also see Section 7.0 for treatment modifications for hematologic and non-hematologic toxicity.**

6.9.1 Potential Adverse Events

Reversible or permanent alopecia, bone marrow toxicity, skin reactions, and esophagitis are expected side effects of radiation therapy. Radiation-induced myocarditis or transverse myelitis rarely occur at doses lower than 50 Gy. Radiographic evidence of radiation change and subsequent fibrosis of the lung will occur within lung volume receiving □ 20 Gy, usually within the first 6-12 months after initiation of treatment. It is essential to spare as much normal lung as possible in order to minimize symptomatic lung injury. If there is a decline in Zubrod performance status to ≥ 2 for greater than 2 weeks while under treatment, radiotherapy should be held with no further chemotherapy administered. Patients should be evaluated closed for prompt resumption of radiotherapy; every effort should be made to limit treatment breaks to 3 days or less.

6.9.2 Esophagitis

Esophageal complaints are common with combined modality therapy. Esophagitis does not constitute a reason to interrupt or delay radiotherapy or chemotherapy provided oral intake is sufficient to maintain hydration. Patients should be advised to avoid alcoholic, acidic, or spicy foods or beverages. Viscous Xylocaine, Carafate, or other medications should be used for symptomatic relief. Occasionally, narcotics may be required. It is not necessary to biopsy acute esophagitis in the first 2 weeks of combined therapy since it is rarely due to underlying viral or fungal disease. Acute esophagitis may persist for 4-6 weeks. If Grade 4 esophagitis occurs, and a treatment interruption is being considered, every effort should be made to limit it to 3 treatment days or less. Patients requiring hospitalization because of esophagitis may have their treatment interrupted. In this event, please notify Dr. Kong.

Esophagitis should be graded according to CTCAE, v. 4.0. The incidence of severe acute esophageal toxicity is expected to be lower than 5%. Since only RILT is modeled by the lung dosimetry, doses to the lung will not be adjusted if excess severe esophageal toxicity occurs. Instead, the normalization dose to the esophagus will be adjusted if at least 2 of the first 10 patients, or 4 of the first 20 patients, or 5 of the first 30 patients experience severe acute esophageal toxicity as described.

Esophagitis Grading System

Grade	Clinical Description
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic; altered eating/swallowing; oral supplements indicated
3	Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated
4	Life-threatening consequences; urgent operative intervention indicated
5	Death

Treatment should be interrupted for grade 4 or greater dysphagia or odynophagia. Acute esophageal toxicity, which typically can occur within 2 weeks of the initiation of treatment and manifests as dysphagia, odynophagia, reflux symptoms, etc. should be pharmacologically

managed with the following approach and should be initiated at the first signs or symptoms of esophageal toxicity.

Suggested Management of Radiation Esophagitis

1. Ketoconazole 200 mg PO q day OR Fluconazole 100 mg PO q day until the completion of radiation;
2. Mixture of 2% viscous lidocaine: 60 cc; Mylanta: 30 cc; sucralfate (1 gm/cc): 10 cc. Take 15-30 cc PO q3-4 hrs prn. (Contraindications: patients taking Dilantin, Cipro, Digoxin);
3. Ranitidine 150 mg PO BID (or other H2 blocker or a proton pump inhibitor such as omeprazole) until the completion of radiation;
4. Grade 4 esophagitis: hold RT + chemotherapy until $\leq$ grade 2 or less. A significant portion of patients are expected to experience grade 3 esophagitis.

Treatment of esophagitis varies with the severity of the patient's symptoms; for example, diet adjustment and narcotic management may be sufficient for grade 2 esophagitis. Nutritional support via gastric tube or jejunostomy tube may be initiated upon development of grade 3-4 esophagitis, per mutual preference of the treating physician and patient.

Severe Acute Esophageal Toxicity

Severe acute esophageal toxicity is defined as persistent grade 3 or higher esophageal toxicity occurring within 3 months of the start of radiation therapy, defined as severe dysphagia or odynophagia with dehydration or weight loss > 15% from treatment baseline, requiring a feeding tube, IV fluids, or hyperalimentation. Grade 4 is defined as esophagitis causing life-threatening consequences, such as perforation, obstruction, or fistula formation. Grade 5 is severe esophagitis directly contributing to death. Persistent grade 3 esophageal toxicity is defined as esophageal toxicity dependent on a feeding tube, IV fluids, or hyperalimentation longer than 6 weeks after the completion of radiation therapy.

6.9.3 Radiation-Induced Lung Toxicity

Common radiation lung toxicity includes radiation pneumonitis and fibrosis and pleural effusion.

Traditionally, RILT, which includes clinical radiation pneumonitis and clinical fibrosis, is defined in the table below and should only be diagnosed after exclusion of infection, tumor progression, and other etiology for the clinical symptoms.

	Clinical Pneumonitis	**Clinical Fibrosis**
Grade 1	Minimal or mild symptoms of **dry cough** and/or **dyspnea** on exertion, without evidence of tumor progression or other etiology, with **radiographic evidence of acute pneumonitis**	**Radiographic evidence of radiation fibrosis** without or with minimal dyspnea
Grade 2	**Persistent dry cough** requiring narcotic antitussive agents or steroid, and/or dyspnea with minimal effort but not at rest, without evidence of tumor progression or other etiology, with **radiographic evidence of acute pneumonitis, and requiring steroid for treatment**	**Radiographic evidence of radiation fibrosis** causing **dyspnea** with minimal effort but not at rest, not interfering with activities of daily living
Grade 3	**Severe cough**, unresponsive to narcotic antitussive agent and /or dyspnea at rest, with **radiographic evidence of acute pneumonitis**, and **requiring oxygen** (intermittent or continuous) for treatment	**Radiographic evidence of radiation fibrosis** causing **dyspnea** at rest, interfering with activities of daily living, and home oxygen indicated
Grade 4	**Radiation pneumonitis** causes respiratory insufficiency, requiring assisted	**Radiation fibrosis** causes respiratory insufficiency, requiring assisted ventilation

	ventilation	
Grade 5	**Radiation pneumonitis** directly contributes to the cause of the death	**Radiation fibrosis** directly contributes to the cause of the death

Severe RILT

Severe lung toxicity includes grade 3 or higher radiation pneumonitis and grade 3 or above clinical fibrosis, as described above, which cannot be explained by another etiology, such as tumor progression or infection.

Suggested management for acute radiation pneumonitis includes bed rest, bronchodilators, and corticosteroids. Oxygen and even assisted ventilation may be necessary for severe cases.

Other Severe Lung Toxicity

- Massive hemoptysis: Hemoptysis causing hemoglobin reduction requiring blood transfusion or causing life threatening condition that cannot be explained by tumor recurrence or pulmonary embolism;
- Bronchial stenosis without evidence of tumor recurrence per PET scan or endoscopic biopsy.

6.10 FMISO-PET/CT Scan (10/17/12)

Note: If a site has access to FMISO, the site is strongly encouraged to participate in the FMISO-PET/CT imaging component. If the site opts to participate, all patients enrolled by the site must receive the FMISO-PET/CT until the required sample size of 58 patients for this component is reached. For institutions participating in the FMISO-PET/CT imaging component, see the RTOG 1106/ACRIN 6697 sample consent.

Patients must be scanned on PET/CT scanners that have been qualified by the ACRIN PET Core Laboratory per the protocol-specific instructions posted on the ACRIN web site at: www.acrin.org/CORELABS/PETCORELABORATORY/PETQUALIFICATION/tabid/485/Default.aspx.

A dedicated PET/CT scanner is mandatory. The PET/CT scanner must be capable of performing both emission and transmission images in order to allow for attenuation-corrected PET images. The ability to calculate standardized uptake values (SUVs) is also mandatory. A flat palette imaging couch is required. Whenever possible, the same scanner should be used for both the FDG-PET/CT and FMISO-PET/CT.

The PET/CT scanner calibrations should be routinely verified according to manufacturer recommendations. The scanner should be assessed regularly for quantitative integrity and stability by scanning a standard quality control phantom with the same acquisition and reconstruction protocols used for study participants. The SUV verification measurements must include the dose calibrator used to measure the doses of study participants to ensure that the dose calibrator and PET scanner are properly cross calibrated, i.e. the dose measured in the dose calibrator and injected into the phantom matches the results obtained from analysis of the phantom images.

A quality control (QC) check must be performed at the beginning of the day for the dose calibrator and well counter, in accordance with manufacturer recommendations. If any of the QC results are outside of the manufacturer's guidelines, the study must be rescheduled and the problem rectified before scanning any patients.

Note: In the event that the FMISO agent becomes unavailable and/or the site is unable to obtain FMISO from Cardinal Health for a consecutive 72-hour period or longer, the potential patients may be offered the opportunity to participate in the trial **without the FMISO-PET/CT** if they are otherwise eligible. **However, site must contact ACRIN Data Management immediately upon notification of unavailability of the FMISO for guidance and instructions for registration and enrollment into the trial.** Once FMISO is available from Cardinal Health, all participants enrolled by the site must receive the FMISO-PET/CT until the required sample size of 58 participants for this component is reached.

6.10.1 Pre-Scan Patient Preparation

- There will be no deliberate fasting prior to injection of FMISO for the participant of this study.
- Patients are encouraged to be well hydrated prior to the scan.
- Blood glucose measurement is not required.
- The patient's height and weight must be measured using calibrated and medically approved devices (not verbally relayed by the patient).

- Vital signs, including temperature, blood pressure, heart rate, and respiratory rate, will be measured prior to injection of FMISO.

6.10.2 Injection of FMISO (2/22/12)

- An IV catheter access line (18 or 20 gauge is preferred) is placed in one arm (ideally contralateral to the tumor side) for the FMISO injection.
- The dose of FMISO will be 3.7 MBq/kg (0.1 mCi/kg) (maximum 260 MBq, 7 mCi) in < 10 mL. For the FMISO injection, minimize the length of the IV tubing between the injection site and the vein to avoid FMISO being left in the tubing.
- A saline flush of at least 10 mL should follow the FMISO injection.
- The exact time of calibration of the dose should be recorded using a global time piece consistently used throughout the study for time recording; the exact time of injection should be noted and recorded to permit correction of the administered dose for radioactive decay. In addition, any of the dose remaining in the tubing or syringe, or that was spilled during injection, should be recorded. The injection should be performed through an IV catheter and 3-way stopcock.
- AEs will be solicited in open-ended fashion (i.e., “how are you feeling?”) at this time.

Note: [^{18}F]Fluoromisonidazole in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Adverse events (AEs) will be evaluated at each imaging session; AE monitoring will cover at least ten half-lives of the FMISO drug, or 24 hours. AEs for FMISO are defined as any signs of illness or symptoms that have appeared or worsened since the infusion of the FMISO. Participants will be queried for potential AEs:

- At the time of injection;
- Before leaving the PET suite;
- If they call the site as instructed for any concerns during the 24 hours after FMISO administration;
- By telephone up to 24 hours post-FMISO infusion.

The AEs that will be specifically monitored during and after the infusion include: localized discomfort at the intravenous (IV) injection site, pain, respiratory difficulties, blood pressure instability, flushing, dizziness, pruritus/rash, and any other symptoms that could be related to an allergic or anaphylactoid-type reaction. When an AE is reported, concomitant medication taken by the participant in the 2 weeks prior to the event and/or during the time of the AE will be collected and documented.

6.10.3 FMISO-PET/CT Imaging

All PET exams should contain 3 trans-axial whole body series, attenuated and non-attenuated, corrected PET and CT images.

- PET/CT imaging of the chest (from the apices to the bases) will occur 2 hours +/- 10 minutes after FMISO injection.
- The patient will empty his/her bladder immediately before the acquisition of images.
- The patient should be positioned on the flat table imaging couch in treatment planning position.
- The transmission scan should be a low-dose CT scan (120-140 kVp, 80 effective mAs) without contrast for the PET/CT and done before the emission imaging.
- A 20-30 minute emission scan of the chest is performed focusing on the area of the primary tumor, with the left ventricle or aorta included in the field of view to be able to measure blood activity. There should be at least 10 minutes per axial field. If greater than 3 axial fields of view are required to cover the lungs, a portion of the lungs may be excluded as far from the primary tumor as possible.
- The blood values for the scans will be derived from a region of interest in a major vessel or cardiac chamber within the field of view.

- Vitals signs, including temperature, blood pressure, heart rate, and respiratory rate, are measured again at completion of the FMISO-PET/CT, and PRN (as needed) through out the procedure.

6.11 18F-fluoromisonidazole (FMISO) (NSC #742836; IND # 76,042)

For complete information, please refer to the current Investigator's Brochure:

[^{18}F]FLUOROMISONIDAZOLE, 1H-1-(3-[^{18}F]-FLUORO-2-HYDROXY-PROPYL)-2-NITRO-IMIDAZOLE, [18F]FMISO AN INVESTIGATIONAL POSITRON EMISSION TOMOGRAPHY (PET) RADIOPHARMACEUTICAL FOR INJECTION AND INTENDED FOR USE AS AN IN VIVO DIAGNOSTIC FOR IMAGING HYPOXIA IN TUMORS. Investigational New Drug (IND) Application IND # 76,042 Edition Number 4, Approval date: 11/09/2009. **NOTE**: to obtain the most current IB contact NCICIPINDAGENTS@mail.nih.gov.

The National Cancer Institute (NCI) is the IND holder for [^{18}F]FMISO (CIP IND # 76,042), which is an investigational radiopharmaceutical PET agent in this study.

6.11.1 Pharmacology and Toxicology

Fluoromisonidazole is a small, water-soluble molecule with a molecular weight of 189.14 Daltons. It has an octanol: water partition coefficient of 0.41, so that it would be expected to reflect plasma flow as an inert, freely-diffusible tracer immediately after injection, but later images should reflect its tissue partition coefficient in normoxic tissues. [^{18}F]FMISO is an azomycin-based hypoxic cell sensitizer that has a nearly ideal partition coefficient and, when reduced by hypoxia, binds covalently to cellular molecules at rates that are inversely proportional to intracellular oxygen concentration, rather than by any downstream biochemical interactions (Prekeges 1991)The covalent binding of nitroimidazoles is due to bioreductive alkylation based on reduction of the molecule through a series of 1-electron steps in the absence of oxygen (McClelland 1990). Products of the hydroxylamine, the 2-electron reduction product, bind stably in cells to macromolecules such as DNA, RNA, and proteins. In the presence of oxygen, a futile cycle results in which the first 1-electron reduction product, the nitro radical anion, is re-oxidized to the parent nitroimidazole, with simultaneous production of an oxygen radical anion. FMISO is not trapped in necrotic tissue because mitochondrial electron transport is absent. The normal route of elimination for FMISO is renal. A small fraction of [^{18}F]FMISO is glucuronidated and excreted through the kidneys as the conjugate.

6.11.2 Toxicity of FMISO in Humans

Since the half-life of fluorine-18 is only 110 minutes, toxicity studies are not possible with the radiolabeled agent. The misonidazole data presented and the [^{19}F]FMISO calculations presented in the Investigator Brochure should be the basis for both animal and human toxicity characterization and conclusions.

6.11.3 Dosimetry

^{18}F is a positron emitter with a half-life of 110 minutes. Intravenously injected [^{18}F]FMISO distributes throughout the total body water space, crossing cell membranes, including the blood-brain-barrier, by passive diffusion. [^{18}F]FMISO is bound and retained within viable hypoxic cells in an inverse relationship to the O2 concentration. The uptake of [^{18}F]FMISO in normal human tissues has been measured and used to estimate the radiation absorbed dose associated with the imaging procedure. Dosimetry studies were performed at the University of Washington and have been published in the peer-reviewed *Journal of Nuclear Medicine* (Rasey 1999).

Sixty men and women were subjects in the study. Of these, 54 had cancer, 3 had a history of myocardial ischemia, 2 were paraplegic and 1 had rheumatoid arthritis. After injecting 3.7 MBq/kg (0.1 mCi/kg), urine and normal tissues distant from each subject's primary pathology were imaged repeatedly to develop time-activity curves for target tissues. All tissues demonstrated a rapid uptake phase and first-order near-logarithmic clearance curves. All tissues receive a similar radiation dose, reflecting the similarity of biodistribution to that of water. Total tissue uptake data were normalized for a 1.0 MBq injection into a 70 kg man (Rasey 1999).

6.11.4 Previous Human [18F]FMISO Imaging Studies

Hypoxia imaging in cancer was reviewed in several recent publications (Raejendran 2005; Rasey 1999; Koh 1995; Raejendran 2004). [^{18}F]FMISO is a robust radiopharmaceutical useful in obtaining images to quantify hypoxia using PET imaging (Graham 1997; Silverman 1998; Rofstad 1999). It is the most commonly used agent for PET imaging of hypoxia (Rischin 2001; Rasey 1999; Koh1995; Raejendran,2004; Valk 1992; Eschmann 2005; Read 1998; Miller 1980). While its biodistribution properties do not result in high contrast images, they result in images at 2 hours after injection that unambiguously reflect regional partial pressure of oxygen, Po_2, and hypoxia in the time interval after the radiopharmaceutical was administered.

6.11.5 [18F]FMISO Administered Dose

[^{18}F]FMISO will be administered to subjects over 1 minute by intravenous bolus injection. The FMISO dose for this protocol should be 3.7 MBq/kg (0.1 mCi/kg) up to a maximum of 260 MBq (7 mCi).

6.11.6 Quality Assurance

Quality Control and Storage: In accordance with regulations, the radioisotope vendor conducts several quality control tests on the [^{18}F]FMISO product prior to release for human administration. Once delivered to the participating institution, doses will be stored in the appropriate storage area in the nuclear medicine facility until they are administered to the patient on the same day.

6.11.7 Supply (10/17/12)

Drug Ordering

[^{18}F]FMISO will be purchased from Cardinal Health (1-614-757-5000), specifically authorized under the NCI IND. The investigator (or appropriate investigator-designee) will order subject doses of [^{18}F]FMISO for this specific trial. Please contact ACRIN to coordinate the ordering of the [^{18}F]FMISO radiopharmaceutical. The investigational radiopharmaceutical [^{18}F]FMISO solution will be shipped to the site the same day the participant is to be injected. FMISO is available under the National Cancer Institute (NCI), Cancer Imaging Program's (CIP's) Investigational New Drug Application (IND) filed with the Food and Drug Administration (FDA). FMISO is supplied by Cardinal Health, which has previously provided NCI with a letter of authorization to cross-reference their Drug Master File filed with the FDA.

Note: In the event that the FMISO agent becomes unavailable and/or the site is unable to obtain FMISO from Cardinal Health for a consecutive 72-hour period or longer, the potential patients may be offered the opportunity to participate in the trial **without the FMISO-PET/CT** if they are otherwise eligible. **However, site must contact ACRIN Data Management immediately upon notification of unavailability of the FMISO for guidance and instructions for registration and enrollment into the trial.** Once FMISO is available from Cardinal Health, all participants enrolled by the site must receive the FMISO-PET/CT until the required sample size of 58 participants for this component is reached.

Sites that are currently synthesize FMISO may synthesize their own FMISO only if their chemistry, manufacturing, and control (CMC) processes and standard operating procedures (SOPs) have already been filed within the NCI IND and have met all requirements in accordance with FDA regulations and guidance.

The investigational pharmacist and/or qualified nuclear medicine technologist at the participating institution will be the responsible party designated by the investigator.

Drug Returns

If for any reason the study imaging is unable to be completed, sites will allow the radioactivity of the [^{18}F]FMISO solution to decay and then discard it appropriately per site's policies and procedures, making a record of the event as required. A copy of the policy should be available upon request.

Drug Accountability

The investigator (or the investigator-designee) must maintain a detailed record of receipt, disposition, and destruction dates of [^{18}F]FMISO solution, using the NCI Investigational Drug Accountability Record Form.

6.12 FMISO Biodistribution and Radiation Dosimetry

The radiation exposure from FMISO in this study will be equal to or lower than that of other widely used nuclear-medicine experimental research agents. Increased voiding frequency will reduce the radiation dose to the bladder wall, which is the organ site that receives the highest radiation absorbed dose. Potential radiation-specific risks associated with this PET study are within generally accepted limits for such studies.

In the dose of FMISO for this study, only a small fraction of the FMISO molecules are radioactive. The amount of injected drug is ≤ 15 µg (≤ 80 nmol per dose) of FMISO. FMISO is administered to subjects by intravenous injection of 10 mL. There is no evidence that nonradioactive and radioactive FMISO molecules display different biochemical behavior.

Tissue	Mean (mGy/MBq)	Mean (mrad/mCi)	Total / 7 mCi (mrad)
adrenals	0.0166	61.4	430
brain	0.0086	31.8	223
breasts	0.0123	45.5	319
gall bladder wall	0.0148	54.8	383
lower large intestine	0.0143	52.9	370
small intestine	0.0132	48.8	342
stomach	0.0126	46.6	326
upper large intestine	0.0140	51.8	363
heart wall	0.0185	68.5	479
kidneys	0.0157	58.1	407
liver	0.0183	67.7	474
lungs	0.0099	36.6	256
muscle	0.0142	52.5	368
ovaries	0.0176	65.1	456
pancreas	0.0179	66.2	464
red marrow	0.0109	40.3	282
bone surface	0.0077	28.5	199
skin	0.0048	17.8	124
spleen	0.0163	60.3	422
testes	0.0146	54.0	378
thymus	0.0155	57.4	401
thyroid	0.0151	55.9	391
urinary bladder wall	0.0210	77.7	544
uterus	0.0183	67.7	474
eye lens	0.0154	57.0	399
Total body	0.0126	46.6	325

Calculated total body dose for a 70 kg man injected with 3.7 MBq/kg was 0.013 mGy/MBq; for a 57 Kg woman it was 0.016 mGy/MBq. Effective dose equivalents (EDEs) were 0.013 mSv/MBq for men and 0.014 mSv/MBq for women. Ninety-seven percent of the injected radiation was homogenously distributed in the body, leaving only 3% for urinary excretion. Doses to smaller organs not directly determined by visualization, such as the lens, were calculated assuming average total-body concentrations. The absence of tracer visualized in images of those organs indicated that accumulation there was not increased. Expected EDE for a 56-kg female is 3.0 mSv (300 mRem) and for a 70-kg male is 3.4 mSv (340 mRem).

More recently, radiation exposure for radiopharmaceuticals has been expressed as the effective dose (ED). The estimated ED for FMISO is 0.015 mSv/MBq . Therefore, for the maximum 7 mCi dose, the maximum emission exposure is 3.9 mSv. For the CT scan of the chest using 120-140 kVp and 80 effective mAs, the maximum transmission exposure is approximately 4.5 mSv, for a combined ED of the emission and transmission components of 8.4 mSv.

6.13 Monitoring for Physiologic Effects of FMISO

6.13.1 Vital Signs

Vital signs, including temperature, blood pressure, heart rate, and respiratory rate, will be measured prior to injection and at completion of FMISO-PET imaging, and PRN (as needed).

6.13.2 Laboratory Studies

No routine laboratory studies are required to monitor FMISO use, but this patient population will have frequent complete blood counts and serum chemistry as part of routine clinical care. These data will not be collected for the study.

6.14 FDG-PET/CT Scan (12/5/12)

Patients must be scanned on PET/CT scanners that have been qualified by the ACRIN PET Core Laboratory per the protocol-specific instructions posted on the ACRIN web site at: www.acrin.org/CORELABS/PETCORELABORATORY/PETQUALIFICATION/tabid/485/Default.aspx.

A dedicated PET/CT scanner is mandatory. The PET/CT scanner must be capable of performing both emission and transmission images in order to allow for attenuation-corrected PET scan images. The ability to calculate standardized uptake values (SUVs) is also mandatory. A flat palette imaging couch is required. Whenever possible, the same scanner should be used for both the FDG-PET/CT and FMISO-PET/CT.

Serial FDG-PET/CT scans of the same patient must be done on the same scanner for this study.

The PET/CT scanner calibrations should be routinely verified according to manufacturer recommendations. The scanner should be assessed regularly for quantitative integrity and stability by scanning a standard quality control phantom with the same acquisition and reconstruction protocols used for study participants. The SUV verification measurements must include the dose calibrator used to measure the doses of study participants to ensure that the dose calibrator and PET scanner are properly cross calibrated, i.e. the dose measured in the dose calibrator and injected into the phantom matches the results obtained from analysis of the phantom images.

A quality control (QC) check must be performed at the beginning of the day for the dose calibrator and well counter, in accordance with the manufacturer recommendations. If any of the QC results are outside of the manufacturer's guidelines, the study must be rescheduled and the problem rectified before scanning any patients.

FDG-PET/CT will be performed in all patients at baseline for staging RT planning and tumor activity assessment. Note that FMISO-PET/CT also will be performed at baseline in such patients, and the baseline FDG-PET/CT must occur on separate days from each other, but in either order. Patients who have already undergone staging FDG-PET/CT at the time of enrollment may need to repeat the FDG-PET/CT in a treatment planning position due to time lapse or image quality issues.

6.14.1 Pre-FDG-PET/CT Patient Preparation

- Prior to injection, the patient must fast for at least 4 hours;
- Patients are encouraged to be well hydrated prior to the scan;
- Blood glucose measurement is required before the injection of FDG and must be < 200mg/dL;
- The patient's height and weight must be measured using calibrated and medically approved devices (not verbally relayed by the patient);

6.14.2 Injection of FDG

- An IV catheter access lines (18 or 20 gauge is preferred) are placed in one arm (ideally contralateral to the side of the primary tumor) for the FDG injection;
- The dose of FDG will be 296-740 MBq (8-20 mCi) depending on institutional procedure and in accordance with manufacturer recommendations;
- A saline flush of at least 10 mL should follow the FDG injection;
- The exact time of calibration of the dose should be recorded using a global time piece consistently used throughout the study for time recording. The exact time of injection

should be noted and recorded to permit correction of the administered dose for radioactive decay. In addition, any of the dose remaining in the tubing or syringe, or that was spilled during injection, should be recorded. The injection should be performed through an IV catheter and 3-way stopcock.

6.14.3 FDG-PET/CT Imaging

All PET exams should contain 3 trans-axial whole body series, attenuated and non-attenuated, corrected PET and CT images.

- Imaging will begin 60 +/- 10 minutes after injection;
- The patient will empty his/her bladder immediately before the acquisition of images;
- The patient will be positioned on the flat table imaging couch in treatment planning position.
- The transmission scan should be a low-dose CT scan without IV contrast (oral contrast is permitted per institutional procedure)for the PET/CT, done before the emission imaging. The transmission scan type, length, etc, should exactly match that used in the calibration and qualification procedure.
- An emission scan from the skull base to thighs at 2-5 minutes per bed position.

6.14.4 Minimum Acceptable Tumor FDG Uptake

If the FDG uptake of the tumor tissue is too low for quantitative analysis (maximum SUV < 4.0), the patient will be removed from participation and replaced with another eligible study patient. In patients whose measurable tumor has a baseline SUV of less than 4.0, a 25% relative decrease of tumor FDG uptake would result in a decrease in SUV of ≤ 1 to the tumor. Data on the test/retest reproducibility of FDG-PET/CT suggest that in an individual patient such a small absolute change in tumor FDG uptake cannot be reliably identified by PET/CT imaging. Therefore, a baseline SUV of at least 4.0 is required for the present study. We expect that the tumor SUV will be less than 4.0 in fewer than 5% of patients. This estimate is based on data on FDG uptake of untreated, advanced NSCLC. SUVs lower than 4.0 are observed in small lesions and in patients with bronchioloalveolar cell carcinomas (BAC).

6.14.5 Adverse Events

Adverse events (AEs) from FDG-PET/CT are exceedingly rare. If an AE from functional imaging is to occur, it would most likely be related to the intravenous catheter infusion site, consisting of erythema and discomfort from the iv. An allergic reaction to the FDG is possible as well. Expected AEs from a PET scan include discomfort and claustrophobia.

6.15 Expected Adverse Events Related to FDG-PET Imaging

6.15.1 Expected Adverse Events from the FDG Injection

- Bruising;
- Bleeding;
- Phlebitis;
- Infection at the site of injection;
- Allergic-type or other adverse reaction to FDG.

6.15.2 Expected Adverse Events from the PET Scan

- Discomfort;
- Claustrophobia

6.15.3 Expected Adverse Events from the CT Scan

- Discomfort;
- Claustrophobia;
- Malfunction of implanted electronic medical devices, e.g., pacemakers, neurostimulators, insulin pumps (see note below).

NOTE: On July 14, 2008, FDA released a preliminary public health notification of possible malfunction of electronic medical devices caused by CT scanning. Sites will use CT scout views to determine if implanted or externally worn electronic medical devices are present and if so, their location relative to the radiation dosage.

PET/CT scanning varies with the part of the body being scanned, the source of the attenuation scan, the timing of the scan, the type of PET imaging being performed, and institution-specific radiation safety policies. The range of exposure for PET/CT scanner can therefore be wide.

6.16 Estimation of Radiation Doses Due to FDG-PET/CT

Reports of radiation doses from PET/CT scanning have varied in the literature. These differences can be attributed to different methods of attenuation correction, the timing of the scan, the area of the body being evaluated, and the radiopharmaceutical being investigated. This research study involves radiation exposure from 2 FDG-PET/CT scans and 1 FMISO-PET/CT scan for a subset of patients. The radiation exposure from each FDG-PET/CT scan is equal to a uniform whole-body exposure of approximately 14 mSv, with approximately 11 mSv from the injected radioactive FDG and 3 mSv from the CT component. CT methods can have a range of radiation doses depending on scanner type and setting and will need to be assessed at each local institution.

6.17 Radiation Therapy/Functional Imaging Adverse Event Reporting (2/22/12)

See Sections 7.9 and 7.12 and Appendix VI for details.