NRG ONCOLOGY
American College of Radiology Imaging Network

RTOG 1106/ACRIN 6697

RANDOMIZED PHASE II TRIAL OF INDIVIDUALIZED ADAPTIVE RADIOTHERAPY USING DURING-TREATMENT FDG-PET/CT AND MODERN TECHNOLOGY IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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

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PARTIAL PROTOCOL—CONTACT ACRIN PROTOCOL DEVELOPMENT AND REGULATORY COMPLIANCE FOR A COMPLETE PROTOCOL

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TABLE OF CONTENTS (12/19/13)

ABBREVIATIONS (8/19/13)

ACRIN: American College of Radiology Imaging Network
AIDS: Acquired Immune Deficiency Syndrome
ASTRO: American Society for Therapeutic Radiation Oncology
ANC: Absolute neutrophil count
AUC: Area under the concentration curve (chemotherapy) or area under the curve (statistics)
BED: Biologic equivalent dose
CMR: Complete metabolic response
CR: Complete response
CTV: Clinical target volume
DLCO: Diffusing capacity of the lung for carbon monoxide
DLT: Dose-limiting toxicities
ECG or EKG: Electrocardiogram
ED: Effective dose
EDEs: Effective dose equivalents
EGFR: Epidermal growth factor receptor
EQD2: Equivalent dose for 2 Gy fractions
FDG: 18F-Florodeoxyglucose, a PET/CT imaging agent
FEV: Forced expiratory volume
FMISO: ^{18}F-fluoromisonidazole, a PET/CT imaging agent
GTV: Gross tumor volume
Gy: Gray
HIV: Human immunodeficiency virus
IGRT: Image-guided radiation therapy
IMRT: Intensity modulated radiation therapy
IV: Intravenous
LRC: Local-regional control
LRP: Local-regional progression
LRPF: Freedom from local-regional progression
MLD: Mean lung dose
MTD: Maximum tolerated dose
MTV: Metabolic tumor volume
NSCLC: Non-small cell lung cancer
NTCP: Normal tissue complication probability
OARs: Organs at risk
OS: Overall survival
PCT: CT from PET/CT
PD: Progressive disease
PET/CT: Positron Emission Tomography/Computed Tomography
PET/CT1: The PCT from the pre-treatment PET/CT
PET/CT2: The PCT from the during-treatment PET/CT
PFS: Progression-free survival
PMD: Progressive metabolic disease
PMR: Partial metabolic response
p.o.: By mouth
PR: Partial response
PTV: Planning target volume
RILT: Radiation induced lung toxicity
RT: Radiation therapy or radiation treatment
RTOG: Radiation Therapy Oncology Group
SD: Stable disease
SMD: Stable metabolic disease

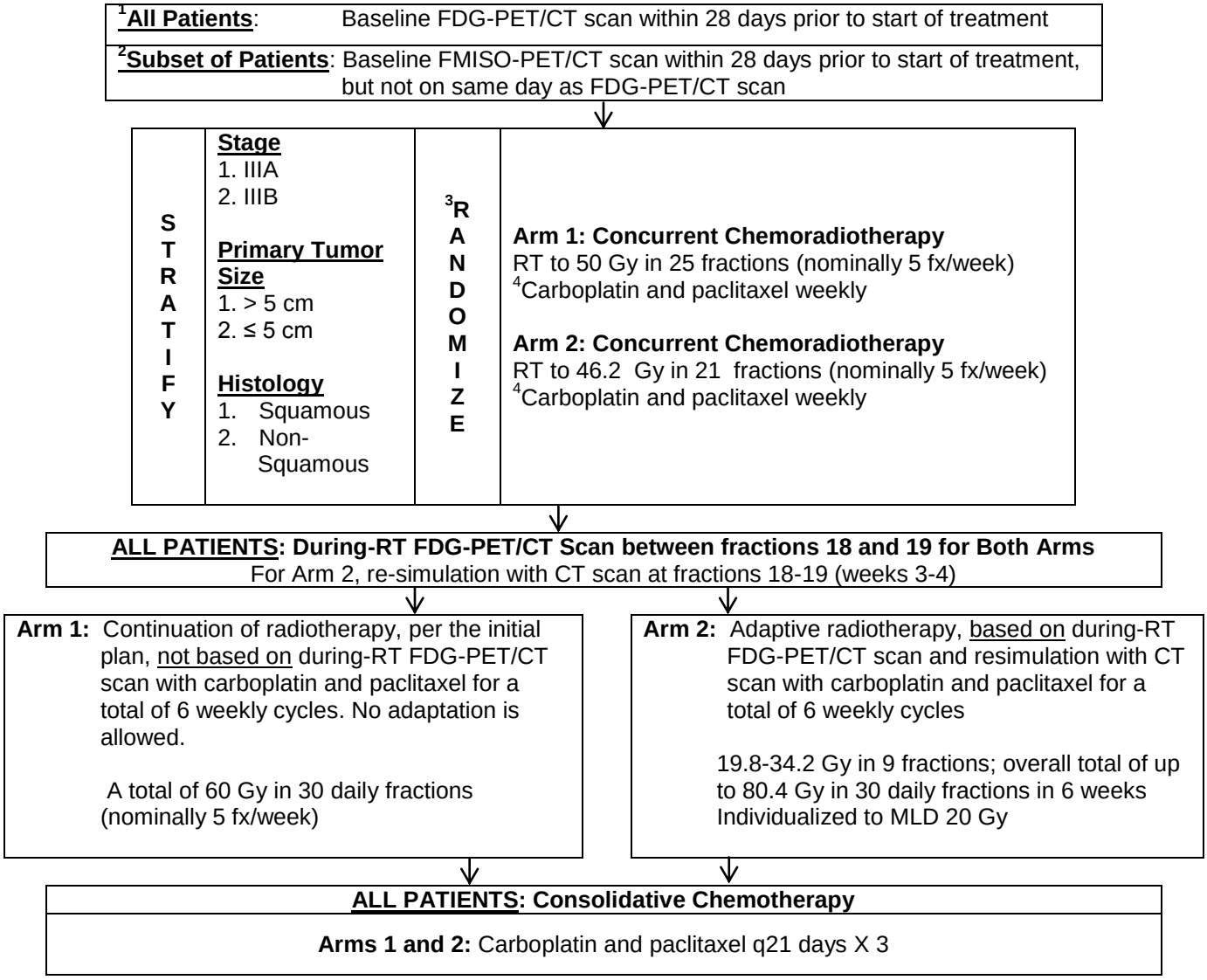
SUV: Standardized uptake value
SUVmax: The SUV of the most intense voxel within a tumor
SUVpeak: The average SUV within a 1.2-cm diameter sphere centered on the most metabolically active region of the tumor
3D-CRT: Three dimensional-conformal radiation therapy
TGF-β: Transforming growth factor beta
TTLRP: Time to local-regional progression
V20: Volume of lung receiving at least 20 Gy
Veff: Biological effective volume

NRG ONCOLOGY
AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

RTOG 1106/ACRIN 6697

Randomized Phase II Trial of Individualized Adaptive Radiotherapy Using During-Treatment FDG-PET/CT and Modern Technology in Locally Advanced Non-Small Cell Lung Cancer (NSCLC)

SCHEMA (8/19/13)



IGRT is mandatory for this study (see Section 5.1).

Continued on next page

[1] **(8/19/13)** All patients will undergo FDG PET/CT at baseline for staging and RT planning and during RT for treatment response assessment and adaptive planning. This baseline scan should be performed within 28 days prior to initiating therapy, while the during-RT scan should be performed between fractions 18 and 19 for both arms. 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. PET/CT will be performed on a flat table top, after at least 4 hours fasting, with controlled blood glucose levels (< 200 mg/dL) and start of imaging acquisition at 50-70 minutes after injection of 8-20 mCi of FDG, in accordance with manufacturer recommendations FDG-PET/CT will be performed in accordance with the protocol and with ACRIN Imaging Standards for PET, http://www.acrin.org/CORELABS/PETCORELABORATORY/PETSOPS.aspx.

[2] **(8/19/13)** Baseline FMISO-PET/CT will be performed only on a subset of patients (n=58) and at institutions with access to the radiopharmaceutical that agree to participate in this imaging component. If the site opts to participate, all patients enrolled by the site must receive the FMISO-PET/CT (when FMISO is available). The baseline FMISO-PET/CT will be performed on a different day before or after FDG-PET/CT, but within 28 days prior to the start of radiotherapy. If pre-treatment FDG-PET/CT is repeated, then FMISO and FDG-PET/CT may be performed in either sequence but must be performed on different days. Institutions that have access to FMISO should participate in the advanced hypoxia imaging of the substudy until target accrual has been reached. **Refer to Sections 6.10–6.13 for detailed information on FMISO and FMISO-PET/CT and Sections 6.14–6.17 for FDG and FDG-PET/CT.**

[3] **(8/19/13)** The randomization of experimental and standard arms is set as 2:1, with stratification by stage, primary tumor size, and histology. The 2:1 randomization will allow more patients to be treated on the experimental arm (Arm 2).

[4] Chemotherapy will begin the same week as radiation therapy and will be given on the same day each week.

Patient Population: (See Section 3.0 for Eligibility)
Patients with FDG-avid and histologically or cytologically proven AJCC stage IIIA or IIIB, non-operable NSCLC

Required Sample Size: 138

ELIGIBILITY CHECKLIST (2/25/14)
(page 1 of 3)

RTOG Institution #
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Case #

____(Y) 1. Does the patient have FDG-avid (maximum SUV ≥ 4.0) and histologically or cytologically proven non-small cell lung cancer?

_____(Y) 2. Does the patient have clinical AJCC stage IIIA or IIIB (AJCC, 7th ed.) non-operable disease? (as described in section 3.1 of the protocol)

__(Y/NA) 3. If the patient has multiple, ipsilateral pulmonary nodules (T3 or T4), is there a definitive course of daily fractionated RT planned?

_____(Y) 4. Did the patient have a history/physical examination, including documentation of weight, within 2 weeks prior to registration?

_____(Y) 5. Was there a FDG-PET/CT scan for staging and RT plan within 4 weeks prior to registration?

_____(Y) 6. Did the patient have a CT scan or sim CT of chest and upper abdomen and a CT scan of the brain or MRI of the brain as specified in Section 3.1?

_____(Y) 7. Were pulmonary function tests, including DLCO, performed within 6 weeks prior to registration and were parameters required in Section 3.1 met?

_____(Y) 8. Was the Zubrod performance status 0-1 within 2 weeks prior to registration?

_____(Y) 9. Was the patient at least 18 years old at the time of registration?

____(Y) 10. Is the patient able to tolerate PET/CT imaging required?

____(Y) 11. Did the patient have a CBC/differential within 2 weeks prior to registration on study with adequate bone marrow function?

____(Y) 12. Did the patient have a serum creatinine within normal institutional limits or a creatinine clearance ≥ 60 ml/min within 2 weeks prior to registration?

_(Y/NA) 13. If the patient is a woman of childbearing potential, was there a negative serum or urine pregnancy test within 3 days prior to registration?

____(Y) 14. Has the patient provided a signed study specific informed consent prior to study entry?

____(N) 15. Does the patient have any component of small cell lung carcinoma?

____(N) 16. Does the patient have any evidence of a malignant pleural or pericardial effusion?

____(N) 17. Has the patient had a prior invasive malignancy (except non-melanomatous skin cancer) and not been disease free for the past 3 years?

____(N) 18. Has the patient had prior systemic chemotherapy for the study cancer?

____(N) 19. Has the patient had prior radiotherapy to the region of the study cancer that would result in an overlap of radiation therapy fields?

____(N) 20. Does the patient have any severe, active co-morbidities as defined in Section 3.2 of the protocol?

Continued on next page

RTOG Institution #
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Case #

____(Y) 21. If the patient is a woman of childbearing potential or a sexually active man, is she/he willing/able to use medically acceptable forms of contraception?

____(N) 22. Does the patient have poorly controlled diabetes (defined as fasting glucose level > 200 mg/dL) despite attempts to improve glucose control by fasting duration and adjustment of medications?

____(N) 23. Is the patient unable to undergo the FMISO-PET/CT?

____(N) 24. If the patient has T4 disease, is there radiographic evidence of invasion of a large pulmonary artery and tumor causing significant narrowing of that artery

Note: The following are required prior to registration:

- IGRT and 3D-CRT or IMRT credentialing;
- A Benchmark credentialing case (planned per Arm 2) must be submitted and approved;

For additional information and/or for clarification on the imaging agents (FMISO and FDG) and/or PET/CT procedures, refer to Sections 6.10–6.17.

The following questions will be asked at Study Registration:

_____ 1. Institutional person randomizing case.

_____(Y) 2. Has the Eligibility Checklist been completed?

_____(Y) 3. In the opinion of the investigator, is the patient eligible?

_____ 4. Date informed consent signed

_____ 5. Patient's Initials (First Middle Last)

_____ 6. Verifying Physician

_____ 7. Patient ID

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnicity

_____ 11. Gender

_____ 12. Country of Residence

_____ 13. Zip Code (U.S. Residents)

_____ 14. Method of Payment

_____ 15. Any care at a VA or Military Hospital?

Continued on next page

ELIGIBILITY CHECKLIST (9/23/13)
(page 3 of 3)

RTOG Institution #
RTOG 1106
Case #

_____ 16. Calendar Base Date

_____ 17. Randomization date

_____ 18. Medical Oncologist's name

_____(Y/N) 19. Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 20. Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 21. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 22. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

_____(Y/N) 23. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?

_____(Y/N) 24. Specify use of IMRT.

_____ 25. Specify the patient's Stage (IIIA vs. IIIB).

_____ 26. Specify the patient's Primary Tumor Size (> 5 cm vs. ≤ 5 cm).

_____ 27. Histologic Type (squamous cell carcinoma vs. non-squamous cell carcinoma)

_____(Y/N) 28. Is the site participating in the ACRIN FMISO imaging component?

_____(Y/N) 29. Patient consent to participate in the ACRIN FMISO imaging component?

_____(Y/N) 30. Is the patient able to undergo the FMISO PET/CT?

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Role of Radiation in NSCLC

Lung cancer is the leading cause of cancer death in the United States and worldwide. In 2010, there were an estimated 222,520 new cases of and 157,300 deaths related to lung cancer in the United States, of which 80% to 85% were non-small cell lung cancers (NSCLC) (Jemal 2010). The majority of patients with NSCLC are medically inoperable or have unresectable disease at the time of diagnosis, because of the presence of locally advanced disease (40%), distant metastases (40%), or co-morbid conditions (Schaake-Koning 1992; Perez 1987). Radiation therapy (RT) is the principal mode of treatment for medically inoperable patients with early stage disease and an important local treatment for unresectable locally advanced disease. Frequently, RT is required for palliative purposes for patients with stage IV disease. It is estimated that 64% of patients require RT at least once, with about 45% receiving it as part of their initial treatment during the course of disease for NSCLC (Tyldesley 2001).

1.2 Local-Regional Control and Overall Survival

Despite advances in radiation technology, treatment outcomes remain poor, and local tumor failure remains a major problem after radiation-based non-surgical treatment. Using modern techniques, current radiation therapy applies a uniform dose prescription of 60 Gy or slightly higher and generates local control rates of less than 50% and a 5-year overall survival rate of ~10-15% (Dillman 1996; Sause 2000; Kong 2005). After RT with or without neoadjuvant chemotherapy, a University of Michigan trial reported ultimate local failure in 70% of patients (Kong 2005). After neoadjuvant chemoradiotherapy in CALGB 9433, 90% of patients ultimately failed locally, with 45% having local failure alone (Kong 2005; Dillman 1996). After neoadjuvant and concurrent chemotherapy with radiation doses of 60-74 Gy, Socinski, et al. (2001) reported that 46% of patients initially had local failure. Evaluation by bronchoscopy and biopsy 1 year after treatment completion revealed pathologic local control rates of only 15%–17% after 65 Gy of radiation with neoadjuvant therapy (Le Chevalier 1994). After chemoradiation with RT doses of 60 Gy in 2 Gy daily fractions or to 69.6 Gy in 1.2 Gy twice a day, a secondary analysis of 11 RTOG trials (9/11 had concurrent chemoradiation) in 1,356 patients reported 2-year and 5-year survival rates of 38% and 15%, with 2-year and 5-year local-regional failure rates of 46% and 52%, respectively (Machtay 2010).

Local-regional disease not only leads to death due to local effects within the chest, but also can serve as a source for metastatic dissemination. Local tumor control or local-regional control (LRC) is not clearly defined in NSCLC. These 2 terms have been used interchangeably in the literature. For the purposes of this study, LRC is defined as freedom from local-regional progression as detailed in Section 1.8.3. LRC correlates with overall survival. In patients with locally advanced disease, Arriagada, et al. (1997) concluded that the main cause of failure is the absence of local control, and local progression or relapse correlated with poorer survival. In RTOG 73-01, the death rate in patients with intra-thoracic failure was similar to that in patients with distant metastases, and increased survival was observed in patients with complete tumor response (Schaake-Koning 1992; Perez 1987). In the CHART trial, local control rates of 20% and 29% were associated with median survivals of 9.9 months and 27.9 months, respectively (Saunders 1999). In an EORTC trial, Schaake-Koning, et al. (1994) demonstrated a similar correlation between LRC and survival. Reviewing mature results of all randomized phase III trials with inclusion of concurrent chemoradiation (Auperin 2010), 10 of 13 reported local or local regional control along with overall survival; the relationship between LRC and survival rates are plotted in Figure 1 below.

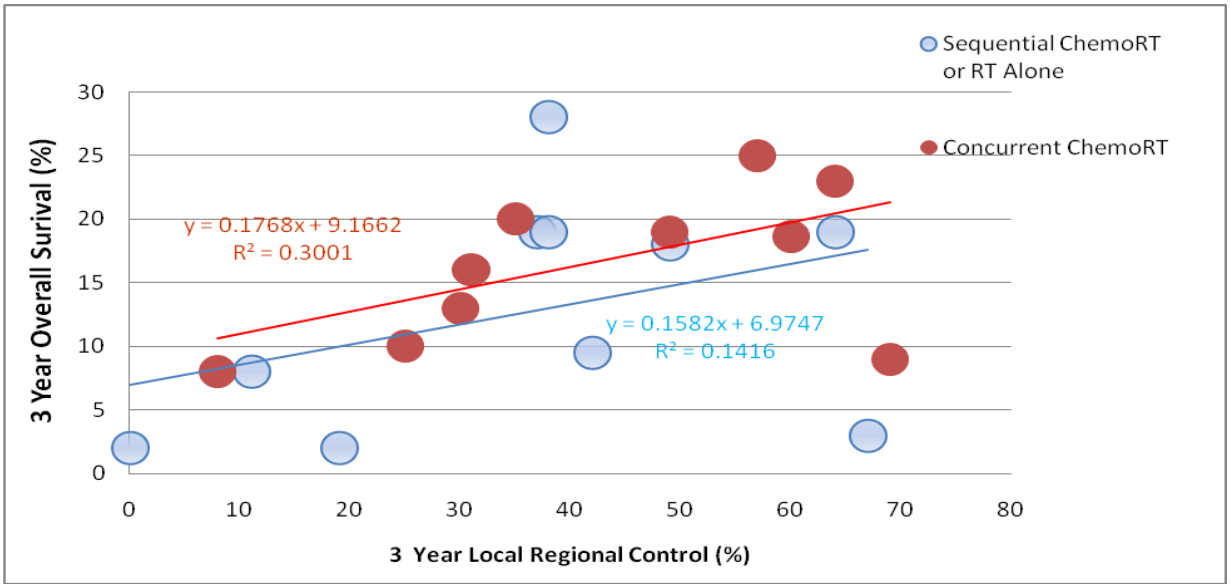

Figure 1: Correlation Between Local Regional Control And Overall Survival
Data presented are reported individual results from 10 phase III trials testing concurrent chemoradiation.

1.3 High-Dose Radiation: Challenges and Potential (8/19/13)

High-dose radiation has the potential to improve local-regional control and overall survival after fractionated therapy. However, it is challenging to deliver a high dose in the majority of patients with locally advanced NSCLC. Modern radiation therapy and adaptive radiation therapy using functional imaging and modern technology may provide the ability to escalate tumor dose without increasing normal tissue toxicities.

1.3.1 High-dose radiation Improves Local-Regional Control and Overall Survival

RT dose is an important factor for local tumor control and perhaps survival in NSCLC. A good example is the long-term result from a phase I study of radiation dose escalation based on isotoxicity bins (UMCC 9204) from the University of Michigan. A total of 122 patients with inoperable/unresectable newly diagnosed or recurrent stage I-III NSCLC were enrolled. Using three-dimensional conformal RT (3D-CRT) and limiting the lung volume irradiated, 106 patients were treated with 63 to 103 Gy in 2.1 Gy fractions. With a median follow up of 8.5 years, median survival was 17 months, and 5-year overall survival was only 13%. Multivariate analysis revealed that radiation dose (p=0.0006) was the most significant predictor for survival. The 5-year survival rates were 4%, 22% and 28% for patients receiving 63-69 Gy, 74-84 Gy, and 92-103 Gy, respectively. The 5-year local control rates were 12%, 35%, and 49% for 63-69 Gy, 74-84 Gy, and 92-103 Gy, respectively. Patients who received more than 74 Gy had significantly better survival. With each 1 Gy increment of radiation dose, 5-year local control improved by 1.25% and the risk of death decreased by 3% (Kong 2005).

For early stage NSCLC, after fractionated RT alone, a study from Washington University at St Louis demonstrated that tumor volume is the most significant factor for tumor control outcome in NSCLC, and patients receiving ≥ 70 Gy had a significantly better local control than those who received < 70 Gy (Bradley 2002). University of Michigan investigators demonstrated that high-dose radiation is more important for patients with larger tumors and may be effective in reducing the adverse outcome associated with a large GTV. A recent analysis of 114 patients with medically inoperable node negative NSCLC showed that there was a significant interaction between radiation dose and GTV ($p < .001$). In patients with a biologic equivalent dose (BED) ≤ 79.2 Gy (physical dose of 66 Gy in 2 Gy daily fractions) [n=68], the median overall survival for patients with GTV > 51.8 cm^3 (~4cm) and ≤ 51.8 cm^3 was 18.2 and 23.9 months, respectively ($p = .015$). If the BED was > 79.2 Gy (n=46), no significant difference was seen between GTV groups ($p = .681$). For patients with GTV > 51.8 cm^3 (n=45), the median overall survival (OS) in those with a BED > 79.2 Gy and ≤ 79.2 Gy was 30.4 and 18.2 months, respectively ($p < 0.001$). For patients with a GTV ≤ 51.8 cm^3 (n=45), the difference was not significant ($p= 0.577$). This study suggested that radiation dose is more important for patients with larger tumors and may be effective in reducing the inferior tumor control outcome associated with larger GTVs (Zhao 2007) in stage I NSCLC.

RT dose also is a significant factor for patients with stage III NSCLC treated with combined chemoradiation. After neoadjuvant chemoradiation in stage III patients, investigators from Memorial Sloan Kettering Cancer Center reported that patients who received ≥ 64 Gy had better survival than those who received < 60 Gy (Rengan 2004). Proportional hazards regression of 237 patients with stage III NSCLC treated with radiation +/- chemotherapy between 1992 and 2002 at the University of Michigan showed that BED was a significant prognostic factor associated with the risk of death (HR=0.96 for each Gy, 95% CI: 0.95-0.97, p < 0.001). For patients who received concurrent chemotherapy, the hazard ratio of BED for the risk of death was 0.97 per Gy (95% CI: 0.95-0.99, p=0 .013). One Gy of dose escalation was associated with a 3% reduction in the risk of death. BED remained a significant independent prognostic factor in patients treated with chemoradiation in the dose range of 60-66 Gy (HR=0.91, 95% CI: 0.84-0.99, p=0.041) [Wang 2008]. Recently, in an RTOG secondary analysis, 1,356 patients treated with chemoradiation between1988 to 2002 were analyzed for BED (1,348 for tBED = treatment time adjusted BED) effect in the dose range of 60 Gy in 2 Gy fractions and 69.6 Gy in 1.2 Gy fractions. The 2-year and 5-year OS rates were 38% and 15%, respectively. The 2-year and 5-year local-regional failure rates were 46% and 52%, respectively. The BED (and tBED) was highly significantly associated with both OS and local-regional failure, with or without adjustment for other covariates on multivariate analysis (p < 0.0001). A 1-Gy BED increase in radiotherapy dose intensity was statistically significantly associated with approximately 4% relative improvement in survival (HR for death=0.96) and 3% relative improvement (HR=0.97) in local-regional control (Machtay 2010).

In summary, radiation dose escalation may improve LRC and OS in patients with stage III NSCLC. Results from several centers (Kong 2005; Bradley 2002; Rengan 2004; Wang 2006) and an RTOG secondary analysis (Machtay 2010) of over 1,300 cases treated with chemoradiation in the dose range of 60-70 Gy have demonstrated that high-dose radiation is associated with improved LRC and OS. Regarding the dose effect in patients who received >70 Gy with concurrent chemoradiation, investigators from University of Michigan recently showed results in the dose range of 60-100 Gy with concurrent and adjuvant carboplatin and paclitaxel (Kong ASTRO 2011). The median local-regional, progression-free survival (95%CI) was 10.7 (Range: 8.4-13.0) months and was not reached (14.1 to date), (p=0.001) for physical doses <70 and >70 Gy, respectively. The median survival was 15.5 (Range: 6.5-24.4) and 41.9 (Range: 18.3-65.5) months (p=0.003), for physical doses less than and greater than 70 Gy, respectively.

RTOG 0617, currently accruing patients, was expected to compare the results between patients treated with 60 Gy and 74 Gy in stage III NSCLC; however, as a result of a planned interim analysis of RTOG 0617, the high-dose radiation arms were closed in June 2011. These arms crossed a futility boundary and will not result in superior survival compared to 60 Gy in this trial. At this time, there does not appear to be any difference in toxicity between the arms of 0617. The reason for the failure of the high-dose arms to show a survival difference in 0617 remains uncertain. Queries about the differences in the high versus standard radiation arms are ongoing and will likely result in a better understanding of the reasons for failure. There are a few key differences between the proposed study, RTOG 1106, and RTOG 0617:

1. RTOG 1106 will limit the duration of radiation therapy to 6 weeks compared to 7.5 weeks of conventionally fractionated doses in RTOG 0617;
2. RTOG 1106 will incorporate a during-RT PET/CT-adapted boost that will allow safe dose escalation for larger tumors, which will benefit more from high-dose RT;
3. All patients in RTOG1106 will have a pre-treatment PET/CT scan within 4 weeks from the start of RT, while in RTOG 0617, PET/CT was neither mandatory nor confined to a particular timeframe;
4. Motion management, including four-dimensional treatment planning, will be required for tumor motion management, image guided radiation therapy (IGRT) will be used for accurate treatment delivery; both of which were not required for RTOG 0617;
5. Radiation dose will be individualized in RTOG 1106 so that the doses to the normal structures are controlled in each patient, while RTOG0617 provided uniform dose prescription disregarding the doses volumes to the normal organs;
6. The radiation oncology investigators enrolling patients will be credentialed, ensuring accurate target delineation and appropriate plan assessment, allowing very close central RT review of compliance of the first 2 patients enrolled from each institution.

1.3.2 Challenges for Radiation Dose Escalation

However, due to limitations of normal tissue tolerance, a significant number of patients cannot receive an adequate dose for tumor control, even with the use of highly conformal techniques. Apparently, radiation induced lung toxicity (RILT) is the most common dose-limiting factor for radiation therapy in NSCLC. With radiation alone or sequential chemoradiation, Michigan investigators reported that the maximum tolerated dose (MTD) of radiation for patients with biological effective volume (Veff) > 0.31 was 65 Gy, approximated to mean lung dose (MLD) of ~20 Gy, from their dose escalation study, UMCC 9204. A total of 109 patients were prescribed protocol RT, with 106 patients completing at least 63.1 Gy, and 84 patients completing > 69 Gy. The trial was stopped at a maximum dose of 103 Gy. With long-term follow up for toxicity, it was demonstrated that much higher doses of radiation than are traditionally administered can be safely delivered to patients with NSCLC when the dose to normal lung tissue is limited. With a mean MLD of 14 Gy (95% CI 4-24 Gy) and a median follow up of 110 months, 17 patients (16%) had grade 2-3 pneumonitis, 15 patients (14%) had grade 2-3 fibrosis, and 17 patients (16%) had grade 2-3 esophagitis. There was no grade 4-5 lung toxicity. Grade 2-3 lung toxicity was not associated with the dose prescribed to the tumor but was significantly ($p < 0.001$) correlated with normal lung dosimetric parameters, such as MLD, volume of lung receiving at least 20 Gy (V20), and the normal tissue complication probability (NTCP) of the entire lung. Using cut-offs of 30% for V20, 20 Gy for MLD, and 10% for NTCP, these factors have positive predictive values of 50-71% and negative predictive values of 85-89% for lung toxicity. There was no significant difference between the models based on mean lung dose and NTCP (Kong 2006). MLD seemed to be a better predictor than NTCP and V20 ($p > 0.05$). Bradley, et al. reported that an MLD-based model is better than other models for radiation pneumonitis, and combining tumor location further improved model accuracy (Bradley 2007).

With concurrent chemotherapy, University of North Carolina (UNC) investigators were the first to report a phase I/II study that escalated radiation dose to 74 Gy with neoadjuvant and concurrent carboplatin and paclitaxel from a starting dose of 60 Gy (Socinski 2001; Rosenman 2002). Limited elective nodal radiation was administered, and all patients received induction chemotherapy before concurrent chemoradiation therapy. Chemotherapy consisted of induction carboplatin (AUC = 6) and paclitaxel (225 mg/m2) for 2 cycles followed by concurrent weekly carboplatin (AUC =2) and paclitaxel (45 mg/m2). Three-dimensional conformal radiation therapy (3DCRT) was delivered in 2 Gy fractions to totals of 60 Gy, 66 Gy, 70 Gy, and 74 Gy. With a median follow-up of 43 months, the median survival was 24 months. The overall survival rate was 50% at 2 years and 38% at 3 years. Based on this study, 74 Gy was judged to be safe in the setting of concurrent chemotherapy.

UNC investigators continued to escalate radiation dose in subsequent trials. Socinski, et al. (2004) reported results of a phase I study that escalated total radiation dose to 78 Gy, 82 Gy, 86 Gy, and 90 Gy, sequentially. Patients on this study received induction chemotherapy (carboplatin AUC = 5, irinotecan 100 mg/m2, and paclitaxel 175 mg/m2 on days 1 and 22. Concurrent weekly chemotherapy consisted of carboplatin (AUC = 2) and paclitaxel (45 mg/m2) beginning with radiation therapy on day 43. These dose levels were achieved without significant dose-limiting toxicities (DLTs). Grade 3 esophagitis occurred in 16%. Three patients developed late esophageal strictures, 2 developed bronchial stenosis, and 2 had fatal hemoptysis. The estimated median survival was 24 months. UNC investigators further reported the results of all 4 sequential prospective phase I/II studies of high-dose (74-90 Gy) 3DCRT in the setting of neoadjuvant and concurrent chemotherapy in 112 patients (Lee 2009). With a median follow-up of 4.9 years for surviving patients, the median survival was 24 months (range 18-31 months). The 1-, 3-, and 5-year overall survival rates were 69% (60-77%), 36% (27- 45%), and 24% (16-33%), respectively. The relatively longer follow-up duration of this population provides information about late complication risks. Among 88 patients who received ≥ 66 Gy, late complications (defined as grade 3 or greater occurring more than 90 days after radiation therapy) occurred in 22% (25/112). Patients with complications appear to have longer survival than the overall group (p=0.007). Late complications included bronchial stenosis (n=3), fatal hemoptysis (n=2), tracheoesophageal fistula (n=1), esophageal stricture (n=7), myocardial infarction (n=5), pericardial disease (n=4), and bone fracture (n=6). The investigators concluded that high-dose thoracic conformal radiotherapy is feasible and results in promising survival outcomes. Late complications occur in a minority of patients. Induction and concurrent adjuvant chemotherapy with 74 Gy 3DCRT generated optimal survival outcome. However, this has not been reproduced by others.

With concurrent and adjuvant carboplatin and paclitaxel and use of a continuous reassessment model for RILT prediction, UMCC 2003-073 intended to accelerate the daily dose 2 days a week to escalate the dose without increasing radiation duration for patients with stage III NSCLC. Among the 18 patients given the protocol prescription, the majority received < 70 Gy due to esophageal or spinal cord constraints (21%) or lung volume limitations (40%), partially due to large tumor volumes. The trial was stopped prematurely due to limited dose escalation.

Dose escalation studies also have been performed in cooperative group trials with concurrent chemotherapy, and this has been found to be challenging in patients with stage III NSCLC. NCCTG 0028 reported that 15 patients received concurrent chemotherapy with weekly carboplatin (AUC = 2) and paclitaxel (50 mg/m2) and 3D-CRT with no elective nodal radiation. No DLTs were reported for the 3 patients who received 70 Gy. One DLT occurred in the 6 patients treated to 74 Gy. Two DLTs occurred in the 4 patients treated to 78 Gy. There were a total of 3 DLTs observed: grade 3 pneumonitis (n= 2) and 1 grade 4 pneumonitis. The MTD of NCCTG 0028 was determined to be 74 Gy. With a median follow up of 28 months, the median survival time was 37 months (Schild 2006). CALGB 30105 evaluated 74 Gy 3DCRT with induction and concurrent chemotherapy in stage IIIA/B NSCLC and reported 24.3 months median survival with induction and concurrent carboplatin/paclitaxel but with an unacceptable high mortality with induction carboplatin and gemcitabine.

With concurrent and adjuvant carboplatin and paclitaxel, RTOG 0117, a phase I/II dose escalation study, reported 2 acute, treatment-related DLTs in the 1st cohort of 17 patients and 6/8 (75%) grade ≥ 3 events during long-term follow up. The protocol was revised to de-escalate the radiation therapy dose (74 Gy in 37 fractions). In the new cohort of 7 patients, treated with 74 Gy, there was 1 DLT in the first 5 patients and no DLTs in the next 2 patients. The MTD was thus determined to be 74 Gy in 37 fractions (2 Gy per fraction) using 3D-CRT with concurrent paclitaxel and carboplatin therapy (Bradley 2010). Both NCCTG 0028 and RTOG 0117 used CT-based, uniform, non-individualized radiation therapy prescription, without the use of modern technology, such as 4D motion assessment and image guided radiation therapy (IGRT).

In summary, it is challenging to deliver high-dose radiation in a majority of patients with NSCLC. Indeed, high-dose radiation often is associated with high risk of radiation toxicity in patients with stage III NSCLC when given with concurrent chemotherapy.

1.3.3 Reduction in Tumor Activity and PET Metabolic Tumor Volume and Potential for Adaptive Dose Escalation with Increasing Doses to Normal Tissue

A series of prospective studies have been performed examining this issue at the University of Michigan. The key findings include the following: 1) NSCLC reduced significantly in FDG uptake and tumor volume during the course of fractionated RT, and such reduction is associated with post-treatment response (Kong 2007); 2) Adapting the planned target volume to this decreased tumor size with a fixed composite NTCP of 15% allows escalation of the total dose by 30-102 Gy (mean: 58 Gy) or a reduction in NTCP of 0.4-3% (mean: 2%) in a limited number of patients (Feng 2009); 3) Metabolic tumor volume (MTV) can be defined reproducibly and a study of 50 patients demonstrated that reduction in MTV was greater than reduction of CT-GTV during-RT (Kong 2010); 4) Using MTV during RT, radiation dose can be escalated above 74 Gy in a majority of patients with stage III NSCLC.

In the initial pilot study of 15 patients, FDG-PET/CT scans were acquired within 2 weeks prior to RT, after the delivery of 45 Gy, and 3 months after completion of RT (Kong 2007). PET/CT scans were evaluated qualitatively by a radiologist and quantitatively for FDG-uptake in regions of interest. Peak activities in primary tumors and in normal lung were determined relative to the mean intravascular background in the aortic arch. MTV was contoured on PET/CT using the same autothresholding value for all scans within each patient. Conformal plans were generated, first using only the pre-RT scans, then adapted to the during-RT MTV. This study demonstrated that the peak tumor FDG-activity decreased significantly during RT after 45 Gy ($p < 0.0001$). The relative peak activities were 5.0 ±2.5, 2.4 ±1.0, and 1.7 ±0.7 in the pre-, during- and post-RT scans, respectively. FDG activity on the during-RT scan correlated significantly with post-RT measures ($R2=0.7$, $p < 0.0001$). Complete metabolic response (CMR) during RT was associated with complete response on post-RT PET and CT scans (Fisher's exact $p=0.009$). There was no significant change in FDG activity in normal lung during RT, although a significant increase was seen on the post-RT PET/CT ($p=0.01$). The mean reduction in MTV was 48±31%, and such reduction was greater than that of CT-GTV. Limited by technology, the

investigators were confident to draw MTVs in 6 out of 15 patients; the dose was escalated in these patients (Feng 2009).

As a part of a validation study and continued research in MTV definition, investigators from University of Michigan almost have completed a second study, UMCC 2006040. Of over 50 patients newly enrolled and studied, the investigators established a reproducible method to delineate MTV and CT-GTV and completed volume analysis in all patients (Kong 2010). The tumor volume reduced significantly during RT on both PET (mean MTV reduction, 95% CI: 69.5%, 62.2-76.8%) and CT images (mean CT-GTV reduction, 95%CI: 41.2%, 32.9-49.6%) with apparently more volume reduction on PET/CT ($p < 0.001$). CT-GTV and MTV were contoured on pre-RT and during-RT PET/CT scans using identical window and level settings. The lungs, heart, esophagus, and cord were contoured consistently between the 2 scans and from patient to patient. Using the same margins for clinical and planning target volumes and the same beam arrangement, 2 plans were generated for each patient based on: A) pre-RT target to 15% lung NTCP and B) pre-RT target to 50 Gy, then adaptation of the plan to the during-RT PET/CT target to a 15% lung NTCP (or equivalent dose for 2 Gy fractions (EQD2) of 100 Gy in 2 Gy daily fractions or other maximum dose constraints specified by the protocol). In patients with very small tumors (less than 100 cc), the dose for 15% NTCP based on the original tumor already was above 100 Gy EQD2, in which case further dose escalation may not have been clinically meaningful; the adaptive plan allows a reduction of doses to adjacent tumors. For patients with larger tumors, dose could be escalated by an average of 20 Gy for tumor.

1.4 Duration of Radiation Therapy and Local-Regional Control

Another problem with traditional dose escalation using conventional fractionation schedules is that the overall treatment time increases considerably. The RTOG 0617 high-dose arm extended treatment duration of 10 days with dose escalation of 14 Gy. Traditional dose escalation using 2 Gy daily fractions would extend treatment duration up to 10 weeks for 90-100 Gy. Extension of treatment duration may allow tumor re-population and decrease the probability of local tumor control and survival. In RTOG 83-11, the dose associated with the highest survival was 69.6 Gy, rather than higher dose levels, in which patients often had extended treatment duration from breaks in treatment due to acute esophagitis. Indeed, survival rates at 2 and 5 years were significantly better in patients who completed treatment in the planned time as compared with those who had treatment interruptions (24% vs. 13% at 2 years and 10% vs. 3% at 5 years) [Cox 1990]. In a large phase III trial reported by Saunders, et al. (1999), 563 patients were randomized into 2 groups treated with either standard RT (60 Gy in 2 Gy fractions, Monday through Friday in 6 weeks) or continuous hyperfractionated accelerated RT (CHART, 54 Gy delivered over 12 consecutive days). Two-year survival was superior in the CHART arm (29% vs. 20%; $P = .008$) despite its lower BED (72 Gy for the conventional arm versus 62 Gy for CHART). It is conceivable that the improved survival with CHART was a result of the decreased overall treatment time. ECOG 2597 compared 64 Gy in 32 fractions over 6.5 weeks with hyperfractionated accelerated radiation therapy (HART) [57.6 Gy/36 fx/3 weeks] after induction chemotherapy in locally advanced, stage III NSCLC and reported a trend toward improved survival in the accelerated arm (Belani 2005). An early analysis estimated that the tumor control probability of NSCLC decreases 1.6% per day after a six-week duration of RT (Fowler 2000). In a secondary analysis of 3 RTOG trials in patients with stage III NSCLC who were treated with immediate concurrent chemoradiotherapy, prolonged treatment time was significantly associated with poorer survival (Machtay 2005). The latter translated into a 2% increase in the risk of death for each day of prolongation in therapy. Thus, every effort should be made to limit treatment duration and avoid treatment delays. Currently, there are investigative efforts to increase daily fraction size to escalate total radiation dose without extending the treatment duration. One approach involves dose escalation using 2.25 Gy daily fractions (once or twice daily) while limiting treatment duration to 6 weeks (Belderbos 2003). This approach was used to escalate to 87.8 Gy in patients with limited lung volumes without concurrent chemotherapy. Another approach is to use a higher fraction dose every day while limiting the treatment duration to 5 weeks without concurrent chemotherapy (Mehta 2001). UMCC 200373 and UMCC2007123 limited treating duration to 6 weeks for RT dose escalation with concurrent chemotherapy, and achieved promising results.

1.5 FDG-PET/CT for Radiation Treatment Planning and Adaptive Planning

FDG is the only Medicare approved PET/CT tracer for cancer imaging and is the most widely available PET/CT procedure used in daily oncology practice. FDG-PET/CT is being used increasingly for management of the disease, including diagnosis, staging, radiation treatment planning, and monitoring treatment response (Borst 2005; Eschmann, 2006; Hicks 2005; Gagel 2006; Juweid 2006; Pottgen 2006).

FDG-PET/CT improves staging accuracy, providing a 20-30% improvement in specificity and sensitivity over CT scanning (Toloza 2003; Rodriguez 2007; Yi 2008). FDG-PET/CT plays an important role in target delineation in radiation treatment planning for NSCLC (Nestle 2005; Yu 2009; MacManus 2009; Gong 2006; Lavrenkov 2005; Bradley 2004). Use of FDG-PET/CT improves the accuracy of target definition (Chapman 2003; Macmanus 2009; Nestle 2006). For the primary tumor, FDG-PET/CT helps differentiate tumor from collapsed lung and/or adjacent normal tissue, such as large vessels, and defines disease extent in the chest wall. PET scans reduced the inter-observer variability compared to CT alone [Fowler 2000). Integrated PET/CT scans further improved delineation consistency (van Baardwijk 2007b). PET helps in finding CT-undetected or borderline sized nodes and improves target accuracy for nodal radiation. A prospective clinical trial using PET/CT-based planning reported isolated nodal failures in only 1 of 44 patients (DeRuysscher 2005b) The tumor target defined from a PET/CT scan is usually smaller than that of a CT scan; therefore, the incorporation of PET/CT into radiotherapy planning has a potential to allow radiation-dose escalation without increasing side effects (DeRuysscher 2005b; van Der Wel 2005). Tumor volume can be generated reliably either by a rigorous visual method (Bayne 2010) or source-to background, ratio-based auto delineation (van Baardwijk 2007); the latter also showed a good correlation with pathology. MTV after chemotherapy or radiation therapy is not well defined. Whether a radiation dose increase will ultimately lead to higher cure rates is the ultimate objective of the proposed study.

In this randomized phase II trial, we will repeat PET/CT and CT simulation during RT around 40-46 Gy EQD2, and in the experimental arm, will redefine the treatment target based on this PET/CT scan, as in UMCC 2007-123. The total dose for each patient in the experimental arm, limited to 100 Gy EQD2, for an alpha/beta of 10 will be determined by the dose corresponding to a MLD of 20 Gy (equivalent to a 15-17% probability of grade > 2 lung toxicity based on the current NTCP model. We hypothesize that the during-treatment, PET/CT-based adaptive therapy will allow us to dose escalate (i.e. raise the daily dose to the reduced target volume for the remainder of the treatment) in the majority of patients and meet the dose limits of normal structures, thus improving LRC without increasing normal tissue toxicity. This also will allow us to use the lung dose limits to individualize adaptive dose escalation to residual active tumor regions and limit the incidence of pneumonitis and other toxicities simultaneously.

1.6 FDG-PET/CT for Treatment Response Assessment

FDG-PET/CT is frequently used to monitor the response of tumors to treatment (Rege 2000; Choi 2002; Jeong 2002; Chapman 2003; Hicks 2004). A high standardized uptake value (SUV) for FDG in the primary tumor and regional nodes after completion of radiotherapy predicts poor treatment response and tumor control (Jeong 2002). A return of tumor SUV to normal values after treatment appears to be an accurate marker for complete response and a sensitive indicator of good prognosis (Rege 2000). The detection of residual and recurrent disease by FDG-PET/CT has a reported sensitivity of 100%, specificity of 92%, positive predictive value of 92%, negative predictive value of 100%, and diagnostic accuracy of 96% (Jeong 2002). The value of FDG-PET/CT in monitoring treatment response was highlighted in a review published in *The New England Journal of Medicine* (Juweid 2006).

Much previous work has been performed in the use of FDG-PET/CT to evaluate response to anti-cancer therapies; these data suggest that early metabolic changes post-therapy are strongly predictive of clinical outcome in many disease states. The literature on FDG-PET/CT has been focused on scans performed at approximately 3 months after completion of radiation therapy (RT). A multicenter study (ACRIN 6668) evaluating the correlation between FDG PET/CT findings approximately 3 months after completion of chemoradiotherapy for NSCLC has completed enrollment, though results are not yet available. However, evaluation of post-treatment images is significantly complicated by the presence of variably hypermetabolic inflammatory post treatment changes. Images done during the course of chemoradiation have shown markedly less inflammatory changes, suggesting that during-treatment FDG-PET/CT may allow a less confounded evaluation of response to therapy. Most importantly, it would be desirable to assess response to therapy during the treatment course as this would permit a change in therapy in patients who are not responding optimally to therapy.

Limited studies have demonstrated that an early (1-2 months) post-treatment FDG-PET/CT scan is a prognostic factor for survival and is more predictive than CT response, stage, or pretreatment performance status (Hicks 2004; Mac Manus 2005). Most recently, interest has increased in performing FDG-PET/CT early during the course of treatment. The change in FDG uptake early during the course of chemotherapy was found to be predictive of progression-free and overall survival (Weber 2003; Nahmias

2007; Hoekstra 2005; de Geus-Oei 2007; Dimitrakopoulou-Strauss 2007). Researchers from the Netherlands reported a large intra-individual heterogeneity in the evolution of FDG uptake during the early course of RT (van Baardwijk 2007). They reported a non-significant increase in the first week (p=0.05) and a small but statistically significant decrease in the second week (p=0.02) during RT. University of Michigan investigators have demonstrated a greater and more significant reduction of peak FDG activity at 40-50 Gy (4-5 weeks during the course of fractionated RT) (Kong. 2007). The regions of peak tumor FDG activity during-RT correlated with those seen 3 months post-RT ($R^2 = 0.7$; $p < .001$). More recently, groups from Stanford University (RSNA 2008) and Princess Margaret Hospital (ASTRO 2008) also studied the role of FDG-PET/CT during RT and reported a heterogeneous reduction of FDG uptake at about 4 weeks during RT. The Stanford group also reported a correlation of FDG uptake during RT with progression-free survival. Indeed, the role of PET/CT in therapeutic monitoring and prediction of outcome is expanding rapidly because of its ability to provide earlier and more robust identification of non- or poor responders than is provided by conventional CT. Therefore, PET/CT potentially can provide important benefits to individual patients by allowing early changes to alternative, more efficacious treatment or by avoiding the unnecessary toxicity related to ineffective therapy. However, knowledge is still limited regarding assessment using FDG-PET/CT scans obtained during RT to predict long-term LRPF and OS in patients with NSCLC.

1.7 Hypoxia PET/CT (FMISO-PET/CT)

Numerous in vivo and in vitro studies have shown that the oxygen tension within solid tumors influences the ability of the cells to respond to radiation therapy. Hypoxia in malignant tumors can affect the outcome of anti-cancer treatments. Oxygen is believed to act as a potent radiosensitizer and hypoxic tumors are relatively resistant to radiotherapy because of their lack of oxygen. In addition, hypoxia triggers several processes such as angiogenesis and enhanced glycolysis that may lead to more aggressive clinical behavior and broad therapeutic resistance. However, proven noninvasive methods to determine the degree of hypoxia within these tumors are not currently available.

Considerable efforts have been put forth to develop methods and imaging techniques for measuring oxygen/hypoxia in tissues. PET/CT has been used for several years as a non-invasive imaging technique to study tumor hypoxia with several radiotracers in development. Radiolabeled 2-nitroimidazole compounds offer a minimally invasive (requiring only an intravenous catheter), less technically demanding technique compared with the gold standard Eppendorf electrode method. Additionally, because all sites of disease can be imaged, the sampling bias inherent in electrode methods is not present with 2-nitroimidazole PET/CT. [18F]Fluoromisonidazole (FMISO) was proposed as a tracer for determining tumor hypoxia in vivo with PET in 1984. Several experimental and clinical studies have indicated that FMISO uptake in tissues is correlated with tissue oxygen tension. Therefore, FMISO-PET/CT allows non-invasive differentiation between hypoxic and normoxic tumors. FMISO has been shown to selectively bind to hypoxic cells both in vitro and in vivo. It has been used to quantitatively to assess tumor hypoxia in different tissues in lung, brain, and head-and-neck cancer patients (Rajendran 2006; Lin 2008).

As hypoxia is one of the most important prognostic factors in cancer of the head and neck (HNC) and NSCLC, Eschmann, et al (2006) examined whether FMISO uptake could predict tumor recurrence after radiation therapy in 14 patients with NSCLC, with additional scans of patients with HNC. At 4 hours after injection, tumor-to-mediastinum (T/M) (or tumor-to-muscle) ratios were used to quantify uptake, and the kinetics of FMISO uptake were described by time-activity curves to stratify patients into defined groups. These results showed that a tumor-to-muscle cutoff of 1.6 in HNC or a tumor-to-mediastinum ratio cutoff of 2 in NSCLC could differentiate those patients who subsequently developed disease recurrence from those who did not. Only 3 out of 11 patients (27%) with ratios less than these cutoff values developed recurrent disease. FMISO-PET demonstrated the ability to image and quantify hypoxia. Tumor cells exhibiting hypoxia were more resistant to radiation therapy than adequately oxygenated tumor cells. The researchers found that high uptake of FMISO correlated with greater risk of tumor recurrence. They also found that a high ratio of uptake of FMISO by tumor tissue compared to uptake by muscle tissue correlated with a higher rate of tumor recurrence. In the work performed by Gagel, et al in an NSCLC population, FMISO-PET allowed for the qualitative and quantitative definition of hypoxic sub-areas that may correspond to the sites of local recurrences. The degree of FMISO uptake may predict response to radiotherapy and freedom from disease, as well as overall survival.

1.8 Rationale and Hypothesis for the Proposed Study (8/19/13)

In summary, RT, as the mainstay of local treatment for inoperable/unresectable NSCLC, has not generated an optimal LRC, despite significant advancement in radiation technology. The majority of patients ultimately develop local-regional failure. Data from matured RTOG studies, University of Michigan, and others have demonstrated that 1) high-dose radiation may be associated with improved LRC either with radiation alone or combined chemoradiation; 2) Limiting treatment duration to 6 weeks may improve tumor control; and 3) MLD is significantly correlated with risk of RILT, and MLD to 20 Gy is considered a relatively safe lung limit. Limited by MLD, a significant portion of patients cannot receive an adequate dose for tumor control, even with the use of highly conformal techniques, particularly with concurrent chemoradiation. Although the excessive lung dose may sometimes associate with the proximity of tumor to critical structures, the most common reason is large tumor size. Recent studies from University of Michigan demonstrated that there is a significant decrease in tumor size and FDG activity at 45 Gy during a course of fractionated radiotherapy. Adapting the planning target volume to this decreased tumor size with a fixed composite MLD of 20 Gy (lung NTCP of ~17.2% for > grade 2 lung toxicity) allows remarkable escalation of the total dose to the tumor. In the experimental arm of this trial, we will repeat CT simulation and FDG-PET/CT at 39.6 Gy and redefine the treatment target based on this FDG-PET/CT scan. The total dose for each patient, limited within the range of 80.5-103.6 Gy BED, will be determined by the dose corresponding to an MLD of 20 Gy. Radiation will be given once a day, 5 days a week, for a total of 30 fractions in 6 weeks. The initial daily fraction will be 2.2 Gy. Daily doses for the adaptive phase will range from 2.2 Gy to 3.8 Gy. We hypothesize that the during-RT, FDG-PET/CT-based adaptive therapy will allow us to raise the daily dose to the reduced target volume for the remainder of the treatment in the majority of patients and meet the dose limits of organs at risk (OARs), thus improving LRC without increasing normal tissue toxicity. This also will allow us to use the lung dosimetry to individualize initial and adaptive RT, provide dose escalation to active tumor regions, and limit the incidence of pneumonitis simultaneously.

1.8.1 Promising Results from Individualized Radiation Dose Escalation to Isotoxicity

University of Michigan has conducted 2 consecutive prospective dose escalation trials to test a hypothesis that radiation dose can be escalated safely above 74 Gy when the radiation dose prescription is individualized at the beginning (UMCC 2003-073) and adapted to the reduced MTV on during-RT FDG-PET/CT (UMCC 2007-123). The prescription dose of the first trial was individually set to correspond to a 15% risk of RT-induced lung toxicity (RILT) according to a NTCP model at the baseline. RT dose was further escalated in the second trial by adapting dose individually to the residual metabolic volume on FDG-PET/CT obtained during RT, so the residual metabolic volume would receive the maximal dose that would maintain a tolerable risk of RILT while the pre-RT CTV on CT was not compromised (would receive at least 60 Gy). All the RT was delivered in 30 daily fractions, 5 days a week for both trials. Fraction size, total EQD2, and biologic equivalent dose (BED) ranged from 2 to 3.8 Gy, 66 to 100 Gy, and 79.2 to 120 Gy, respectively. Carboplatin and paclitaxel were given concurrently and adjuvantly. Of 18 patients treated on the first trial, the median EQD2 delivered was 66 Gy (range: 66-100); only 7 patients received ≥ 74 Gy EQD2. With a minimum follow up of 50 months and with a mean GTV of 288 cm^3 (17-648), these patients had a median and 5-year overall survival of 30 months and 33%, respectively. Twelve patients died: 5 from local failure, 3 with distant metastasis, 3 of heart disease, and 1 with radiation pneumonitis. Six patients were alive: 1 with local progression and 5 with no evidence of disease at the last follow up. Patients treated to a higher dose had significantly better survival (p=0.02). For toxicity, 5 patients (22%) had grade ≥ 2 RILT, and 10 patients (55%) had ≥ grade 2 radiation esophagitis. As of May 2010, a total of 40 patients consented for UMCC 2007-123; 34 patients enrolled. Six patients were taken off study: 4 due to findings of distant metastasis on planning FDG-PET/CT; 2 due to other reasons. The median EQD2 delivered was 100 Gy (range 80-100) [p < 0.01 comparing to mean dose of the 1st trial], 26/30 received > 74 Gy EQD2 within 6 weeks; 20 received the maximum trial dose of 100 Gy EQD2, including the first 5 of 6 patients with a minimum 18-month follow up, without evidence of local disease progression or dose-limiting RILT. Thirty-two patients completed RT; 20 patients had at least 6 months follow-up, and 25 patients had 3 months follow up. There were 5/32 cases (16%) of ≥ grade 2 radiation lung toxicities (pneumonitis or fibrosis) and 9/27 cases (31%) of > grade 2 esophagitis. There were 3 deaths: 1 sudden death with unknown etiology at 2 years with no evidence of tumor recurrence; 1 death at 6 months from GI bleeding with the presence of gastric and esophageal ulcers; 1 death at 10 months from multifocal pneumonia (radiation-related toxicity cannot be ruled out). Median overall and local regional progression-free survivals have not yet been reached.

1.8.2 Feasibility Testing: Multi-Center Dry-Run Planning Study

We recognize that the proposed trial is complex and requires standardization of target delineation and individualized adaptive RT planning. We have completed 2 Dry-Run dosimetric studies using with 4 sets of FDG-PET/CTs (2 sets of pre-during scans) from patients treated on UMCC 2007123. A third Dry-Run study is in process.

The first Dry-Run case was tested by 14 centers (11 RTOG member institutions), including testing of the reliability of mid-treatment MTV and competence of generating an adaptive plan. Despite use of various types of software, the majority of centers generated safe plans meeting the study requirements and dose constraints of organs at risk.

The variations in MTVs were not significantly different from CT-GTVs of primary tumors and nodal diseases either pre- or during-RT (p=NS). However, variations of these volumes were remarkable, ranging 1.4 to 9.2 fold of maximum over minimum for individual targets. Nodal CT-GTV pre-RT and CT-GTVs during-RT had the greatest variation, with a magnitude above 5 fold of maximum over minimum. During-RT GTV and MTV had greater variations than those of pre-RT ones, with during-RT CT-GTV having the greatest difference from one physician to another. There also were remarkable variations in OAR volumes, with maximum up to 4 fold greater than minimum for 1 structure.

Using during-RT PET/CT and with some individual instruction, 11/11 RTOG institutions were capable of generating an adaptive plan to escalate PTV doses. Plan A (conventional plan) generated a mean PTV dose of 73.3 Gy (95% CI 73.2-74.2) with MLD of 20.3 (95% CI 19.3-21.3) Gy. The PTV dose of plan B (individualized adaptive plan) was escalated to a mean of 83 Gy (95% CI 81-85), with an MLD reduced to 19.0 Gy (95% CI 18.3-19.2), decreases in the means of mean esophageal, heart V40, esophageal V60, and maximum cord doses, and a small increase (0.8 Gy) increase in the maximum esophageal dose. All adaptive plans had an MLD < 20 Gy. Figure 2 shows the detailed dosimetric differences between plan Bs and As of the individual centers. This Dry-Run study demonstrated that despite significant variations between target and OAR volumes, there are no significant differences in variations between CT-GTVs and MTVs on either pre- or during-RT scans. Adaptive planning is feasible among RTOG centers to provide relatively consistent PTV dose escalation and OAR dose reduction.

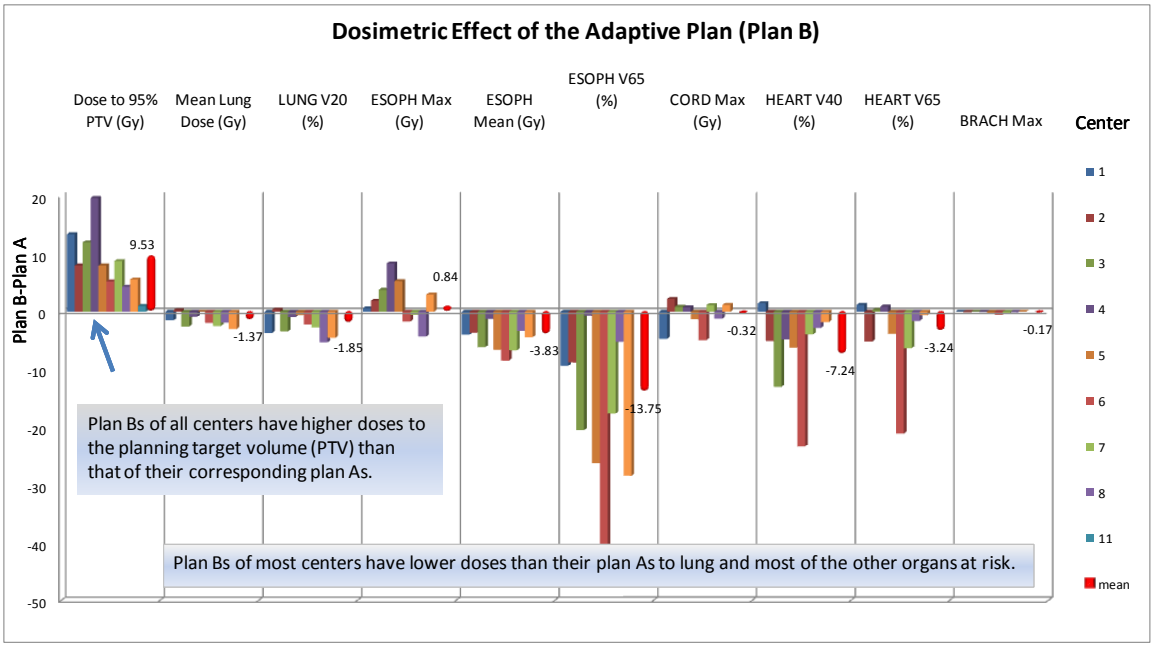

Figure 2: Doses to PTV and OARS
from 11 RTOG Institutions from the first Dry-Run case.

A second Dry-Run study also was completed among 11 RTOG institutions. The participating centers were given more detailed instructions regarding the target delineation and an atlas of normal structures (Kong 2010).

The variations of GTV and MTV were less than that of the first Dry-Run case, ranging 1.6 to 4.0 fold of maximum over minimum (1.2 to 7.2 for the first case). During-RT GTV and MTV still had greater variations than those of pre-RT ones; Compared to results of the first Dry-Run case, the during-RT CT-GTV from the second Dry-Run case had the greatest difference from one center to another. There were some notable reductions of volumes in the esophagus and heart, but similar level of variations were seen in the spinal cord and brachial plexus.

The dose escalation from the second Dry-Run case was much more uniform than that of the first Dry-Run case. All 11 RTOG institutions were capable of generating an adaptive plan to escalate PTV doses above 82 Gy. Plan A (conventional plan) generated a mean PTV dose of 73.7 Gy (95% CI 72.8-74.8) with a MLD of 19.1 (95% CI 18.0-20.6) Gy. The PTV dose of plan B (individualized adaptive plan) was escalated to a mean of 86 Gy (95% CI 84-87), with a MLD reduced to 18.0 Gy (95% CI 16.5-18.6), decreases in the means of mean esophageal, heart V40, esophageal V60, and maximum cord doses, and the maximum esophageal dose. All adaptive plans had a MLD < 20 Gy. Figure 3 shows the detailed dosimetric differences between plan Bs and As of the individual centers. Most importantly, the time it took to complete the second Dry-Run case was remarkably shorter than that of the first Dry-Run study.

The second Dry-Run study demonstrated reduction of variations in target and OAR volumes and more uniform PTV dose escalations. This suggests the value of the Dry-Run exercises. We are in the process of completing a third Dry-Run case by the same centers. We will generate consensus atlas from this case, which will be serve as the gold standard for credentialing Institutions for participation in this trial.

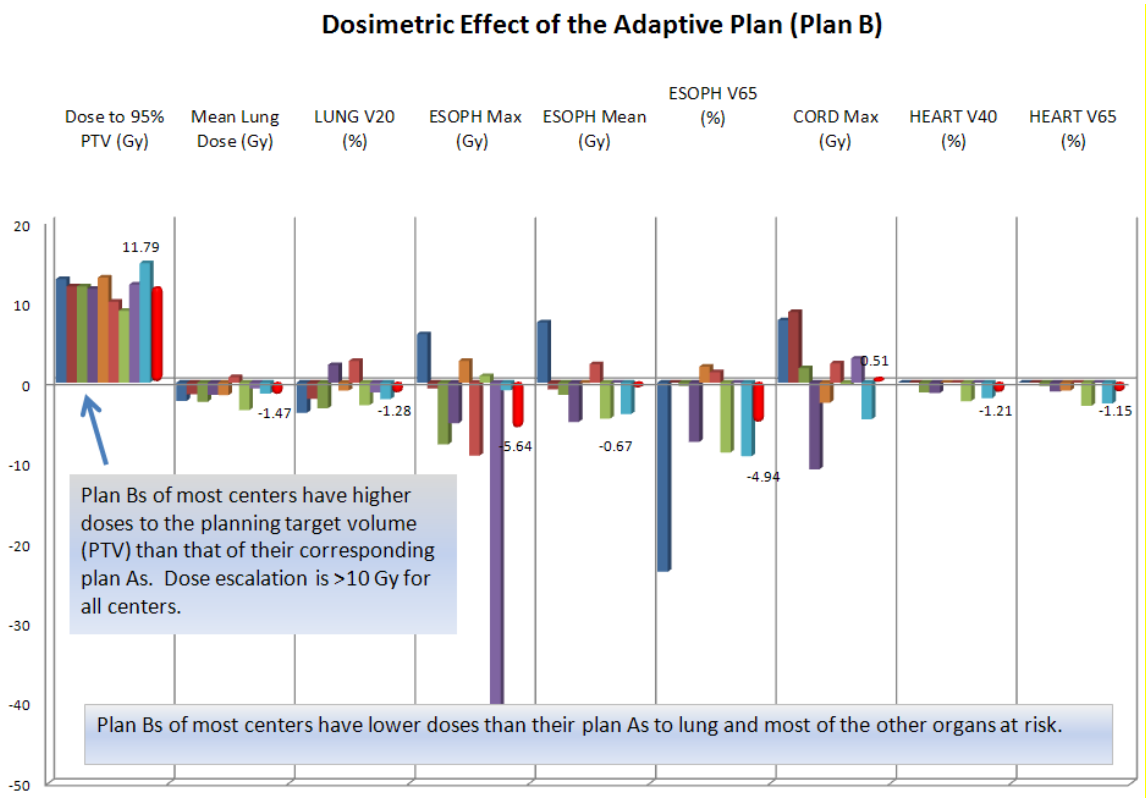

Figure-3: Doses to PTV and OARS from 11 RTOG Institutions from the second Dry-Run case.

1.8.3 Evaluation of Treatment Response

LRC or LRPF is defined as freedom from local-regional progression (LRP). LRP is defined as a development of progressive lung cancer centered within 1 cm from the planning target volume (PTV). Progressive disease in any of the 14 nodal stations will be considered as regional recurrence, even if it is beyond 1 cm of the initial PTV. Assessment of LRP will start at 1-3 months after completion of RT, i.e. LRP on during-RT scans will not be counted, as patients may be treated during the adaptive course of RT. Patients will be censored if/when they die of distant metastases and/or die without documented LRP. Time to LRP will be measured from the date of registration. Progression will be assessed by RECIST 1.1 (Eisenhauer 2009), with integration of FDG-PET/CT. FDG-PET/CT will be used to confirm new sites of disease.

Specifically, an event of LRP must meet the following criteria:

- An increase of at least a 20% in the diameter, with an absolute increase of at least 5 mm of any target lesion (primary tumor or nodal disease), taking as reference the smallest on study measurement (this includes the baseline one if that is the smallest on study). Note: the appearance of one or more new lesions is also considered progression;
- An increase of at least 20% in the peak standardized uptake value (SUVpeak) of any target lesion (primary tumor or nodal disease), taking as reference the smallest measured value on study (this includes the baseline measurement if that is the smallest on study) (Kong 2007); **or**
- New lesions within 1 cm from the initial planning target volume (PTV) or new FDG uptake in any of the nodal regions (more active than mediastinal blood pool), typical of cancer, and not related to treatment effect, infection, or other etiology;
- All findings of local-regional progression will be confirmed pathologically or on a follow-up scan within 1-3 months, and all will be centrally reviewed and confirmed.

1.9 Translational Research

1.9.1 Background

While it seems essential to deliver an adequate dose of radiation with chemotherapy to shrink the tumor for disease control, it is important to note that patients often respond to treatment differently in terms of both tumor control and treatment-related toxicity. With advancements in the field, we have recently learned that the expression of different specific molecules in the tumor can be associated with either various prognoses or with predicting outcomes from certain treatments. Zheng, et al. (2007) and Bepler, et al. (2006) evaluated the prognostic value of the protein expression of excision repair cross-complementation group 1 (ERCC1) and RRM1 (regulatory subunit of ribonucleotide reductase) in tumors of early stage NSCLC treated with surgical resection alone. High expressions of these 2 specific proteins were significantly associated with improved survival. The tumoral RRM1 expression also was a major predictor of tumor response to gemcitabine/platinum chemotherapy (Holdenrider 2006).

1.9.2 Potential Blood Markers Predictive of Treatment Response and Long-Term Outcome

While there is a significant amount of data on biomarkers from tumor tissue specimens (which unfortunately is often unavailable in patients with unresectable disease), there is a short list of blood markers for treatment response assessment or prediction. In a limited number of patients, plasma transforming growth factor beta 1 (TGFß1) level was increased in many patients with NSCLC (Kong 1997), and its level before RT start was correlated with disease status at long term follow up (Kong 1999). Changes in blood nucleosomal DNA fragments, cytokeratin-19 fragments (CYFRA 21-1), ERCC1 protein polymorphisms, or serum carcinoembryonic antigens specifically identified a subgroup of patients with insufficient therapy response at the early treatment phase and was shown to be valuable for disease management (Park 2006; Ardizzoni 2006; Tas 2006). The EGFR mutation status in the blood was consistent with that in the tumor tissue, suggesting a potential value of studying biomarkers in the blood (Moran 2007). Tumors with a higher basal apoptotic rate (not just that induced on therapy) may be more primed to die in response to a pro-apoptotic stimulus (Zhang 2009). Recently, normalizing serum markers of apoptosis (caspase cleaved products of cytokeratin 18 detected via the M30 Apoptosense ELISA) to basal tumor volume determined via volumetric CT has been shown to strongly correlate with M30 fold change following stereotactic body radiotherapy (SBRT) to all known sites of disease (Zhang 2009b). Serum levels of transforming growth factor-alpha (TGFa) and amphiregulin (ARG) were recently reported to be predictive of EGFR-TKI response (Vollebergh 2010). The SWOG0003 study reported that pretreatment plasma levels of hypoxia associated protein osteopontin (OPN) are significantly associated with patient response, PFS, and OS in chemotherapy-

treated patients with advanced NSCLC (Mack 2008). Changes of carcinoembryonic antigen (CEA) or CYFRA21-1 can be used to predict the imaging therapeutic effect and PFS of the patients. (Li 2010). Most recently, a Netherlands study of 106 patients reported statistically significant results for blood CEA, IL-6, OPN, and CYFRA 21-1 ($p = 0.013$, $p = 0.003$, $p = 0.004$, and $p < 0.001$, respectively). Higher biomarker levels were associated with a lower probability of survival. Comparing to a baseline model consisting of gender, World Health Organization performance status, forced expiratory volume, number of positive lymph node stations, and gross tumor volume of an AUC of 0.72, a model including blood level of CEA and IL-6 resulted in a leave-one-out AUC of 0.81. The performance of this model was significantly better than the clinical model ($p = 0.004$). These results were validated in an independent data set from their own study (Dehing-Oberije 2010). This correlative study will validate this model and determine whether a model combing OPN, CEA, CYFRA21, and IL6, as well as imaging factors, will provide better prediction then models of using clinical factors alone.

1.9.3 Potential Blood Markers Predictive of Normal Tissue Toxicity from Radiation

To predict normal tissue toxicities from radiation treatment, plasma transforming growth factor beta 1 (TGFß1) has been most extensively studied for pneumonitis (Kong 2005) and non-lung toxicities (Anscher 1998). Researchers from Duke University reported that the plasma TGFß1 level at the end of radiation correlated with symptomatic lung toxicity in patients treated with definitive radiation therapy (Vujaskovic 2000). Kong, et al. (2000) further demonstrated that loss of a tumor suppressor gene, the mannose 6-phosphate receptor or insulin-like growth factor-2 receptor, contributed to increased TGFß1 levels and subsequent radiation-induced pneumonitis in patients with lung cancer. In patients treated with escalating doses of radiation, Anscher, et al. (2003) found a significant correlation between TGFß1 levels and late non-pulmonary grade 3 radiation toxicity. A recent study from the University of Michigan has shown that radiation induced elevation in TGFß1 levels during the course of external beam conformal radiation therapy is highly correlated with the occurrence of grade > 2 radiation pneumonitis (Zhao 2008). Other cytokines also are involved in lung toxicity. Interleukin-6 (IL-6), a major mediator of the acute-phase inflammatory response, synthesized by a variety of cells in the lung parenchyma including the alveolar macrophages, type II pneumocytes, T lymphocytes, and lung fibroblasts, also has increased mRNA expression in macrophages and a trend toward increased plasma concentrations after thoracic RT (Park 2000). IL-6 actively participates in the inflammatory process of lymphocytic alveolitis (radiation pneumonitis), both in experimental models and in human lung diseases by stimulating inflammatory cells, particularly lymphocytes and macrophages. Chen, et al. (2001) and Damaraju, et al. (2001) reported that pre-treatment IL-6 level may serve as a predictor for radiation pneumonitis. A recent study also showed promising results correlating single nucleotide polymorphisms (SNPs) of several specific genes within white blood cells with radiation induced acute and late toxicities (Chang 2005; Yuan 2009). For example, CT/CC genotypes of TGFß1 rs1982073:T869C genes were associated with a lower risk of RILT in patients with NSCLC treated with definitive (chemo) radiotherapy (Kong 2008b). Recently, University of Michigan investigators studied 5 inflammatory cytokines (IL-1α, IL-6, TNF-α, IL-8, and TGF-ß1) with MLD for prediction of RILT (Stenmark 2009). Of 58 patients reported, 10 (17.2%) developed grade greater than or equal to 2 RILT. Lower pre-treatment IL-8 levels were significantly correlated with the development of RILT while radiation-induced elevations of TGF-ß1 were marginally correlated with RILT. Significant correlations were not found for any of the remaining 3 cytokines or any clinical or dosimetric parameters. Using receiver operator characteristic curves for predictive risk assessment modeling, both individual cytokines and dosimetric parameters were found to be poor independent predictors of RILT. However, combining IL-8, TGF-ß1, and MLD into a single model yielded an improved predictive ability (AUC 0.80, 95% CI 0.66-0.94, $p < 0.001$) as compared to any cytokine or MLD alone. This proposed correlative study will focus on validation of this model.

1.9.4 General Hypothesis

The general hypothesis is that blood cytokine, proteomic, and genomic markers in the blood prior to and during the course of treatment will be correlated with tumor control outcome, which includes response after completion of all treatment, PFS, OS, patterns of failure, and treatment-related adverse events. The primary goal of this correlative translational analysis is to examine whether models of combining any of the cytokine, proteomic, or genomic markers in the blood at baseline and during the course of 3D-CRT with physical dosimetric factors and functional imaging biomarkers can predict tumor control outcome and/or radiation toxicity better than models without the addition of blood markers.

Specifically, we aim to:

- Study whether a model of combining current clinical factors with blood markers such as osteopontin (OPN) (for hypoxia), carcinoembryonic antigen (CEA) and cytokeratin fragment

(CYFRA) 21-1 (for tumor burden), and IL-6 (for inflammation) will predict 2-year LRC and overall survival better than a current model using clinical factors and radiation dose;

- Determine/validate whether a model of combining MLD, transforming growth factor beta1 (TGFβ1) and IL-8 will improve the predictive accuracy for clinical significant RILT better than the current model of using MLD alone;
- Explore in a preliminary manner whether proteomic and genomic markers in the blood prior to and during the early course of treatment, as well as imaging factors, are associated with metabolic tumor response during and after completion of treatment, LRC, PFS, OS, pattern of failure and treatment-related adverse events, such as radiation pneumonitis, esophagitis, and pericardial effusion.

1.9.5 Rationale

Blood circulates in the body and carries molecules released or shed from tumors and normal tissues in response to treatments. Blood has the potential to serve as a surrogate marker for the individual's intrinsic genomic responsiveness of the tumor and normal tissue to radiation. If it works, a blood marker is more advantageous than tissue as it is associated with minimally invasive procedure for sampling and provides an opportunity for repeat testing to monitor treatment response or toxicity. Recent studies have shown correlations of genomic mutations (such as EGFR) between blood and tumor tissue and between expression of certain gene/protein (such as ERCC1) and tumor responses to chemotherapeutic regimens, and blood markers for hypoxia, tumor burden, and inflammation are significantly associated with survival. For radiation toxicity prediction, the levels of cytokine/proteomic markers and presence of certain specific gene polymorphisms in the blood as well as the changes of the levels during and after treatment were correlated with RILT after completion of conventional fractionated 3D-CRT. We anticipate that combining promising blood markers, which reflect both tumor response and lung damage, with current clinical and imaging factors will improve predictive accuracy for clinical tumor control and treatment toxicity.

There are many other molecules involved in the processes of tumor response and radiation normal tissue toxicity. The advances in cytokine arrays, proteomic, and genomic techniques have now made it possible to evaluate many of these proteins and genes together for their association with treatment outcome. Through this multi-center trial, we also will explore the correlation between blood markers pre-, during- and post- treatment and long-term treatment outcome in tumor control and normal tissue complications.

1.9.6 Preliminary Results

Feasibility Study and Setting Up Quality Assurance Measures for a Multi-Center Blood Marker Study

Quality control of specimens is critical to ensure the success of any biomarker study, particularly in a multicenter setting. Lack of quality control of blood sample collection has caused confusion in the literature and impacted TGF-β1 levels and the clinical significance of their ability to predict radiation pneumonitis. We have completed a sample collection study for an optimal and feasible method to obtain plasma samples under the multi-center setting. A standardized blood sample collection and plasma preparation process has been established, not only for TGF-β1 levels, but also for measurement of other cytokines.

Conditions that could introduce platelet contamination/degradation will increase the level of TGF-β1 and other cytokines, and confound the study results. The following are the key findings from the University of Michigan and Duke University Medical Center: 1) Serum samples are not good for cytokine studies, as the blood clotting process alters the physiologic condition, and releases TGF-β1 and other cytokines from platelets and other blood cells. Serum TGF-β1 levels have been reported to be about ten-fold that of the plasma levels; 2) Heparin, an anticoagulant commonly used in the collection of blood samples, will bind to and enhance the activity of antithrombin III, and can often result in a higher TGF-β1 level in plasma due to platelet activation. Use of heparin as an anticoagulant in blood sample collection should be prohibited for measurement of TGF-β1 and other proteins stored in platelets. Ethylenediaminetetraacetic acid (EDTA) does not have a direct effect on platelet activation, thus, can be used as an anticoagulant in blood collection, if special attention is paid to avoid platelet degradation and contamination; 3) Setting blood samples at room temperature can significantly alter TGF-β1 levels in plasma due to platelet degradation. In our study, placing blood at room temperature for half an hour led to an increase in TGF-β1 levels to as high as 140% of the original levels; 4) Longer duration caused more substantial elevation; plasma TGF-β1 levels elevated to 4-10 times higher than their original level after the blood samples were kept at room temperature for 4 hours. Keeping blood samples on ice can

significantly decrease the speed of platelet degradation and increase the reproducibility of cytokine measurement; 5) The centrifugation gravity and duration are also critical for reproducible TGF-β1 measurement. Insufficient centrifugation could cause platelet contamination and a significant elevation in TGF-β1 levels. The variation from various methods reached over 10 times of the original level (from 1.9 to 20.0 ng/mL). Platelet factor 4 (PF4) level was highly correlated with TGF-β1 (Figure 3) and can be used as a reliable surrogate marker for platelet contamination/degradation (kits for the measurement of PF4 are much less expensive).

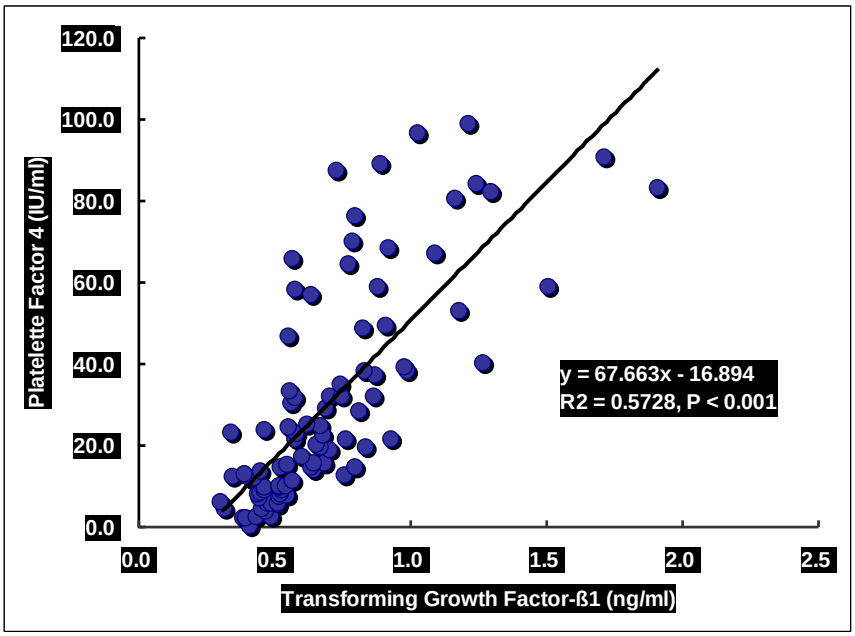

Figure 3: Correlation between plasma TGF-β1 and platelet factor 4. High TGF-β1 level also could be from platelet degradation

We have validated the above results and confirmed an optimal method of blood collection and handling in the multi-center setting with support from the RTOG translational research program and the University Michigan Global Reach Program. In this study, 8 centers collected blood samples and prepared plasma and serum specimens on site based on a given protocol. Prepared samples were sent to the University of Michigan and Peking Union Medical College for PF4 assessment of platelet degradation. The testing centers were blinded for the sample processing method. We have confirmed that inadequate centrifugation and extended blood setting time especially at room temperature and on ice have significantly elevated the plasma PF4 level and generated poorer results. Blood setting in ice for 30 minutes or less provides the most reproducible optimal results for all cytokines (Figure 4). Permitting blood samples to stand at room temperature for 5 minutes caused significant elevation in PF4 levels. Of critical importance, setting blood samples in ice for 4 hours artificially increased the levels of PF4 and TGF-ß1 of some centers but did not change the levels of other cytokines from samples of all centers. We also have established normal levels of 30 cytokines from optimally prepared and assayed samples of healthy volunteers.

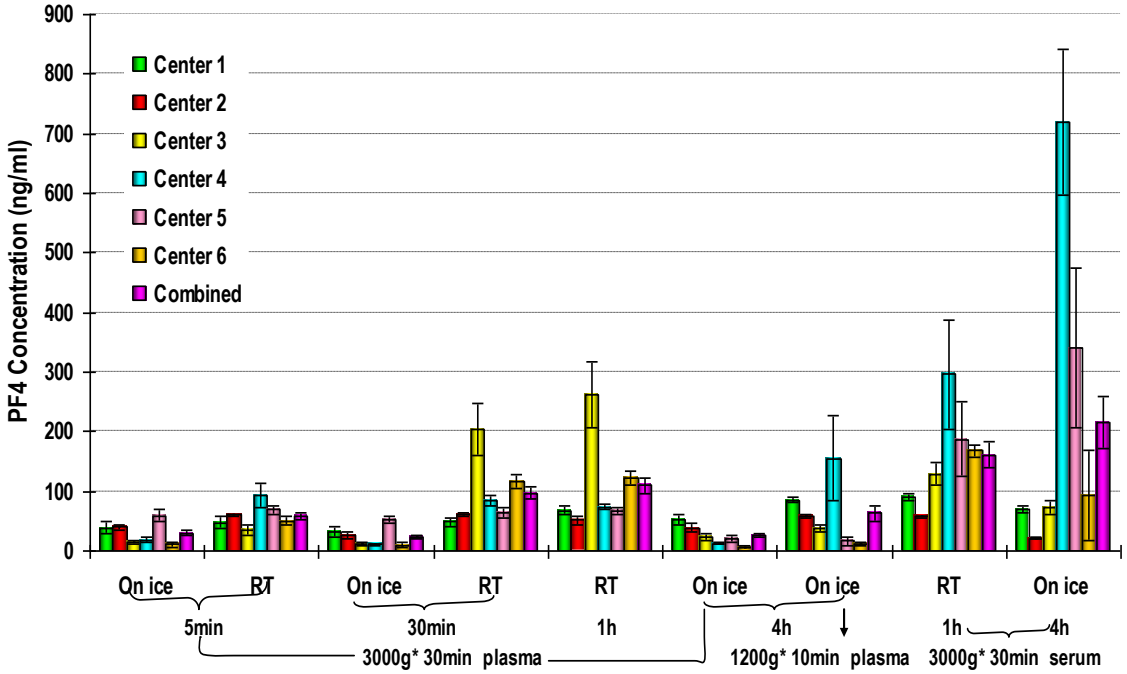

Figure 4: PF4 Results from 6 initial centers suggesting conditions that elevate the level of platelet factor 4 (PF4). Normal plasma PF4 should be around 20-30; higher PF4 indicates platelet activation/contamination. The methods of providing the least platelet activation are the ones with lowest and most reproducible PF4 level: keeping blood on ice for less than 30 min and spinning the blood at 3000xg for 30 min.

In addition to validating the optimal plasma processing method, these results demonstrated the feasibility of this proposed study: collecting blood and preparing plasma samples onsite, delivering specimens, and having standard assays performed in designated centers for reproducible results. We will use the optimal method for plasma sample preparation. The blood samples always should be stored in ice before centrifugation, and should never be left at room temperature. Blood samples should be spun at 3000xg for 30 minutes to obtain platelet-poor plasma for cytokine measurements.

Preliminary Results on Biomarkers for Tumor Control Outcomes

We also have demonstrated that many cytokine levels in the blood are associated with tumor control or survival outcome:

1) Absolute level of plasma TGF-ß1 during follow-up is correlated with recurrent disease (Cai 2009) and single nuclear polymorphism (SNP) of TGF-ß1 at baseline is associated with overall survival;
2) Patients with elevations of plasma Fractalkine and IL-7 at 2 weeks during-RT had better overall survival than patients without. Patients with EGF, Fractalkine, IL-10, IL-1β, IL-2, IL-7 and TGF-α elevation at 4 weeks during RT had better overall survival than patients without (Kong 2008);
3) Baseline CEA, OPN and IL-6 were associated with long-term survival in patients with NSCLC.

Preliminary Results of Lung Toxicity Outcomes

We and others have demonstrated that:

1) Radiation-induced changes in plasma TGF-ß1 at 4 weeks during RT, baseline IL-8 are predictive of post-RT RILT (Chen 2002; Zhao 2009; Stenmark 2009; Ao 2009; Kim 2009; Ao 2008);
2) There are differential changes in proteins associated various pathways between animals sensitive to and resistant to radiation lung damage (Ao 2008);

There are significant differences in at least 5 baseline plasma proteins, such as vitronectin, in a study of 48 patients with and without RILT;

3) All of these proteins are associated with inflammatory pathways; some of them may have remote relationship with TGF-ß1 and IL-1 (Cai 2010).
4) We have demonstrated that from a study 58 eligible patients (Stenmark 2009), a model that combining IL-8, TGF-ß1 ratio of during-/pre-RT (instead of all inflammatory cytokines), with MLD yielded an improved predictive ability (AUC 0.80, 95% CI 0.66-0.94, $p < 0.001$) as compared to MLD alone.
5) Genetic variation of *TGFβ1 -509C/T* may have an association with accumulated thoracic toxicity in lung, esophagus, and pericardium (without inclusion of other cardiac events), while ACE was significantly associated with acute cardiac events (Yuan 2010).

In this multi-center study, we will measure cytokines levels, assess the genomic variation to validate the above predictive model, and explore new models for predicting treatment outcome.

The immediate goal of the correlative study is to explore models for tumor control and validate predictive models for lung toxicity. The intermediate goal is to study biomarkers correlated with other treatment toxicities, such as esophagus and heart. The long-term goal of this biomarker study is to collect and bank biospecimens and collect reliable data for future studies focusing on molecular marker-based individualized care in patients with NSCLC.

2.0 OBJECTIVES

2.1 Primary Objectives (8/19/13)

2.1.1 RTOG: To determine whether tumor dose can be escalated to improve the LRPF rate at 2 years when an individualized adaptive radiation treatment (RT) plan is applied by the use of a FDG-PET/CT scan acquired during the course of fractionated RT in patients with inoperable or unresectable stage III NSCLC;

2.1.2 ACRIN: To determine whether the relative change in SUVpeak from the baseline to the during-treatment FDG-PET/CT, defined as (during-treatment SUVpeak – baseline SUVpeak)/baseline SUVpeak x 100%, can predict the LRPF with a 2-year follow up.

2.2 Secondary Endpoints

RTOG

- To determine whether an individualized dose escalation improves overall survival (OS), progression-free survival (PFS), lung cancer cause-specific survival, and delays time to local-regional progression compared to a conventional RT plan;
- To compare the rate of severe (grade 3+ CTCAE, v. 4) radiation-induced lung toxicity (RILT), as defined in the table below:

Severe RILT (pneumonitis)	**Severe RILT (clinical fibrosis)**
Severe cough, unresponsive to narcotic antitussive agent and /or dyspnea at rest, with radiographic evidence of acute pneumonitis, without evidence of infection, tumor progression or other etiologies, and requiring oxygen (intermittent or continuous) for treatment	Radiographic evidence of radiation fibrosis causing dyspnea at rest, interfering with activities of daily living, without evidence of infection, tumor progression or other etiologies, and home oxygen indicated
Radiation pneumonitis causes respiratory insufficiency, requiring assisted ventilation	Radiation fibrosis causes respiratory insufficiency, requiring assisted ventilation
Radiation pneumonitis directly contributes to the cause of the death	Radiation fibrosis directly contributes to the cause of the death

- To compare other severe adverse events, including grade 3+ (CTCAE, v. 4) esophagitis or grade 2 pericardial effusions, or any grade cardiac adverse events related to chemoradiation between a PET/CT-guided adaptive approach and a conventional RT plan.

ACRIN

- To evaluate the association of baseline FMISO uptake (tumor-to-blood pool ratio) with LRPF (i.e. the assessment of using baseline FMISO-PET uptake as a prognostic marker);
- To determine if the relative change in SUVpeak from baseline to during-treatment FDG-PET/CT and/or baseline FMISO uptake (tumor-to-blood pool ratio) predicts the differential benefit of the adaptive therapy, i.e. the association of uptake parameters with LRPF depending on the assigned treatment. The aim is to assess if these uptake parameters can be useful in guiding therapies, i.e. predictive markers;
- To determine if other PET imaging uptake parameters (SUVpeak during-treatment for FDG-PET, maximum SUV, or relative change of maximum SUVs from pre- to during-treatment FDG-PET/CT, change in metabolic tumor volume, FMISO total hypoxic volume, FMISO tumor to mediastinum ratio, EORTC or University of Michigan/Kong's response criteria) will predict OS, LRPF, and lung cancer cause-specific (LCS) survival as well as to explore the optimal threshold for differentiating responders from non-responders.

2.2.3 Correlative Science Objectives

- To study whether a model of combining current clinical and/or imaging factors with blood markers, including osteopontin (OPN) [for hypoxia marker], carcinoembryonic antigen (CEA) and cytokeratin fragment (CYFRA) 21-1 (for tumor burden), and interleukin (IL)-6 (inflammation) will predict the 2-year LRPF and survival better than a current model using clinical factors and radiation dose as well as imaging factors;
- To determine/validate whether a model of combining mean lung dose (MLD), transforming growth factor beta1 (TGFβ1) and IL8 will improve the predictive accuracy for clinical significant RILT better comparing to the current model of using MLD alone;
- To explore in a preliminary manner whether proteomic and genomic markers in the blood prior to and during the early course of treatment are associated with tumor response after completion of treatment, LRPF, PFS, OS, and pattern of failure and treatment-related adverse events, such as radiation pneumonitis, esophagitis, and pericardial effusion.

3.0 PATIENT SELECTION (12/19/13)

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED. For questions concerning eligibility, contact RTOG Data Management (via the RTOG contact list on the RTOG web site, www.rtog.org).

3.1 Conditions for Patient Eligibility (2/25/14)

3.1.1 Patients must have FDG-avid (maximum SUV ≥ 4.0) (from PET scan of any date, any scanner) and histologically or cytologically proven non-small cell lung cancer.

3.1.2 Patients must be clinical AJCC stage IIIA or IIIB (AJCC, 7th ed.) with non-operable disease; non-operable disease will be determined by a multi-disciplinary treatment team, involving evaluation by at least 1 thoracic surgeon within 8 weeks prior to registration; Note: For patients who are clearly nonresectable, the case can be determined by the treating radiation oncologist and a medical oncologist, or pulmonologist.

3.1.3 Patients with multiple, ipsilateral pulmonary nodules (T3, or T4) are eligible if a definitive course of daily fractionated RT is planned.

3.1.4 Appropriate stage for protocol entry, including no distant metastases, based upon the following minimum diagnostic workup:

- History/physical examination, including documentation of weight, within 2 weeks prior to registration;
- FDG-PET/CT scan for staging and RT plan within 4 weeks prior to registration;
- CT scan or sim CT of chest and upper abdomen (IV contrast is recommended unless medically contraindicated) within 6 weeks prior to registration;
- CT scan of the brain (contrast is recommended unless medically contraindicated) or MRI of the brain within 6 weeks prior to registration;
- Pulmonary function tests, including DLCO, within 6 weeks prior to registration; patients must have FEV1 ≥ 1.2 Liter or ≥ 50% predicted without bronchodilator;
- Zubrod Performance Status 0-1 within 2 weeks prior to registration;

- Age ≥ 18;
- Able to tolerate PET/CT imaging required to be performed at an ACRIN qualified facility;
- CBC/differential obtained within 2 weeks prior to registration on study, with adequate bone marrow function defined as follows:
- Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3;
- Platelets ≥ 100,000 cells/mm^3;
- Hemoglobin ≥ 10.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 10.0 g/dl is acceptable.);

3.1.5 Serum creatinine within normal institutional limits or a creatinine clearance ≥ 60 ml/min within 2 weeks prior to registration;

3.1.6 Negative serum or urine pregnancy test within 3 days prior to registration for women of childbearing potential;

3.1.7 Women of childbearing potential and male participants must agree to use a medically effective means of birth control throughout their participation in the treatment phase of the study.

3.1.8 The patient must provide study-specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility (12/5/12)

3.2.1 Patients with any component of small cell lung carcinoma are excluded.

3.2.2 Patients with evidence of a malignant pleural or pericardial effusion are excluded.

3.2.3 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years (For example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible);

3.2.4 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable.

3.2.5 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;

3.2.6 Severe, active co-morbidity, defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;
- Transmural myocardial infarction within the last 6 months;
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
- Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol.
- Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.

3.2.7 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.8 Poorly controlled diabetes (defined as fasting glucose level > 200 mg/dL) despite attempts to improve glucose control by fasting duration and adjustment of medications. Patients with diabetes will preferably be scheduled in the morning and instructions for fasting and use of medications will be provided in consultation with the patients' primary physicians;

3.2.9 For FMISO-PET/CT: patient is unable to undergo this imaging;

3.2.10 Patients with T4 disease with radiographic evidence of massage invasion of a large pulmonary artery and tumor causing significant narrowing and destruction of that artery are excluded.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations (8/19/13)

4.1.1 A complete panel of electrolytes within 2 weeks prior to treatment

4.2 Highly Recommended Evaluations/Management

Note that these evaluations/interventions are highly recommended as part of good clinical care of patients on this trial but are not required.

4.2.1 Comprehensive pulmonary consultation within 6 weeks prior to start of treatment;
4.2.2 EKG and/or echocardiogram within 6 weeks prior to start of treatment;
4.2.3 Quantitative lung ventilation/perfusion scan +/- CT scan within 6 weeks prior to start of treatment;
4.2.4 Nutritional assessment, including evaluation of the need for prophylactic gastrostomy tube placement (if the patient is ≥ 10% below ideal body weight) within 6 weeks prior to start of treatment.

5.0 REGISTRATION PROCEDURES (12/19/13)

Access requirements for OPEN and TRIAD

Site staff will need to be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account. This is the same account (user id and password) used for the CTSU members' web site. To obtain an active CTEP-IAM account, go to https://eapps-ctep.nci.nih.gov/iam.

Note: This trial is not utilizing the services of the ITC for dosimetry digital treatment data submission. See below for information on installing TRIAD for submission of digital RT data prior to enrolling patients.

Participating institutions must complete all pre-registration requirements before enrolling patients on study. See the table and text below.

Table 5.0: Summary of Required Credentialing (8/19/13)

ACRIN Credentialing		
Credentialing	**Web Links for Procedures and Instructions**	**Phone Number**
Institution	www.acrin.org/CORELABS/PETCORELABORATORY/PETQUALIFICATION	215-940-8890.
Scanner	http://www.acrin.org/CORELABS/NCICQIEQUALIFICATIONPROGRAM/NCICQIEQUALIFIEdscanner.aspx	

RTOG Credentialing (2/25/14)		
Credentialing	**Web Link for Procedures and Instructions**	**Phone Number**
IGRT (Section 5.1) IMRT* (Section 5.2) 3D-CRT** (Section 5.3) Benchmark Case (Sections 5.2, 5.3 and 5.4)	For All: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1106 **Note**: Institutions already credentialed for RTOG SBRT lung trials do not need to repeat credentialing for IGRT and IMRT, unless the institution's technique has changed. These sites only need to do Dry Run/Benchmark credentialing , planned per Arm 2 (see Section 5.4).	For All: 215-574-3219

*All institutions credentialing for IMRT (or 3D-CRT together with gating or tracking) must irradiate the IROC Houston (former Radiologic Physics Center [RPC]) phantom.

** Institutions intending to use IMRT for some cases are required to complete IMRT credentialing but are not required to complete 3D-CRT credentialing. Institutions using 3D-CRT together with gating or tracking for motion management must irradiate the IROC Houston phantom for credentialing (see IMRT credentialing).

5.1 Pre-Registration Requirements for Image-Guided Radiotherapy (IGRT) Treatment Approach

5.1.1 In order to be eligible to enroll patients on this trial, the center must be credentialed for either 3D-CRT or IMRT and the center must be credentialed for lung image-guided radiotherapy (IGRT). Institutions credentialed for IMRT will be allowed to enter patients using 3D-CRT.

Institutions previously credentialed for these treatment techniques will not be required to repeat this step in many situations. Exceptions to this statement are listed in the various subsections below. Institutions that have not been credentialed by the RTOG to perform 3D-CRT or IMRT MUST apply for 3D-CRT or IMRT credentialing as described below in Sections 5.2 and 5.3. **Note**: Centers credentialed for the use of IGRT for RTOG SBRT lung trials are automatically credentialed for IGRT for this trial but must repeat the process if their IGRT technique has changed. Centers credentialed for RTOG 0617 are automatically credentialed for 3D-CRT for this trial provided that the motion management and dose calculation algorithms are approved as per SBRT trials.

5.1.2 IGRT Credentialing Process **(2/25/14)**

IGRT is mandatory for this study. Each center must be credentialed for lung IGRT. IGRT information is available at the following web site:
http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1106

- Each institution will be required to undergo credentialing for lung cancer IGRT before registering patients to this protocol. This involves completion of a Facility Questionnaire and a review of at least 1 case from each institution. The first step in the credentialing process is for the institution to complete a new Facility Questionnaire or modify their existing Questionnaire, which can be found on the IROC Houston (former Radiologic Physics Center (RPC) web site, http://irochouston.mdanderson.org. The second step is to set up a TRIAD account for digital data submission; see Section 5.6.In addition to the general information required for completing this questionnaire, the institution must answer all questions pertaining to IGRT in the section relating to this capability.
- Next, the institution must submit a series of 5 consecutive daily pre-treatment images along with a spreadsheet of IGRT data from an anonymized lung cancer patient. This patient should have a lung tumor similar to the patients that are acceptable for inclusion on this protocol. See http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1106 for the spreadsheet that must be completed for this credentialing step. The accepted pre-treatment image types include three-dimensional (3D) volumetric images (either fan- or cone-beam CT using Megavoltage (MV) or kilovoltage (Kv) x-rays or Orthogonal (MV or Kv) 2D images). These images and the spreadsheet will be reviewed by the Principal Investigator, Feng-Ming (Spring) Kong, MD and/or the Medical Physics Co-Chairs, Randall Ten Haken, PhD, Ying Xiao, PhD, or Martha Matuszak, PhD. Once approved, RTOG will notify the institution by e-mail.

5.2 Pre-Registration Requirements for IMRT Treatment Approach (2/25/14)

Only Required for Institutions Intending to Use IMRT Planning and Delivery

Institutions not intending to use IMRT for any patients entered on this study can go directly to Section 5.3. However, it is important to point out that some of the requirements in Section 5.3 overlap with requirements in this section. When this is the case, Section 5.3 refers the reader back to the relevant sub-section below.

5.2.1 In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available at http://irochouston.mdanderson.org; select "Credentialing" and "Credentialing Status Inquiry".

5.2.2 The institution must complete the following steps to be credentialed for IMRT:

- First, if the institution has not previously met the credentialing requirement for IMRT lung irradiation, the institution must complete relevant sections in the Facility Questionnaire mentioned in Section 5.1.2 above, paying special attention to the sections on 3D-CRT (if the institution will use this treatment modality for some patients) and IMRT. Additionally, the section describing the motion management technique the institution will use for entering patients on this study must be completed. Second, an IMRT phantom study must be successfully completed through IROC Houston. Instructions for requesting and irradiating the phantom are available on the IROC Houston web site at http://irochouston.mdanderson.org; select "Credentialing" and "RTOG". Upon review and successful completion of the phantom irradiation, IROC Houston will notify both the registering institution and RTOG Headquarters that the institution has completed this requirement.

- Third, the institution must generate target and critical structure contours, plus a treatment plan for a Benchmark case. The details for Benchmark testing are provided in Section 5.4. The Benchmark case also serves to verify and credential the institution's ability to register required PET/CT imaging studies with planning CT information. The details of this procedure are provided in Section 5.4. Upon review and successful completion of the Benchmark credentialing, RTOG will notify the institution that the institution has successfully completed this requirement. Fourth, the institution must complete credentialing for motion management. Motion management credentialing is incorporated into the phantom irradiation process. No added credentialing steps are required for most motion management techniques. However, when tracking or gating are employed, the phantom irradiation of IMRT credentialing described in Section 5.2.2 must be completed using a moving phantom supplied by IROC Houston to simulate respiratory motion. Institutions must inform IROC Houston about their motion management technique at the time they request a phantom for the credentialing irradiation. All institutions intending to use IMRT for any of the patients they register to this study must irradiate the IROC Houston phantom for credentialing. As detailed in the next section, institutions using only 3D-CRT for patients registered to this study also must irradiate a phantom under certain circumstances. As outlined in the next section, this exception applies for 3D-CRT as it does for IMRT when institutions use either tumor tracking or beam gating for motion management. Institutions can contact IROC Houston (713-745-8989) for information regarding credentialing associated with motion management.
- Institutions are required to send planning and contouring information for the initial patients they register for treatment on this study for Pre-treatment Review before the start of RT. This step is similar to the Benchmark requirement with one important difference. The Pre-treatment Review cases have to be completed under the restrictions of the short timelines that are necessary to enter patients on this study (see Section 5.4.3).

5.3 Pre-Registration Requirements for 3D-CRT Treatment Approach (2/25/14)

Institutions using 3D-CRT and not intending to use IMRT are required to irradiate a phantom only when the motion management approaches of target tracking or beam gating are used during treatment delivery and an acceptable dose calculation heterogeneity correction algorithm is used. Other institutions treating with 3D-CRT will not be required to perform a phantom irradiation. Please contact IROC Houston to obtain a phantom at http://irochouston.mdanderson.org.

5.3.1 Only institutions that have met the technology requirements and that have provided the baseline physics information my enter patients onto this study.

5.3.2 The institution must complete the following steps to become credentialed for 3D-CRT:

- First, the Facility Questionnaire discussed above must be completed with special attention to the section for 3D-CRT and the section describing the institution's motion management techniques. The questionnaire is available at http://irochouston.mdanderson.org and must be approved by RTOG prior to registering any patients.
- Second, as stated above, when the motion management techniques of target tracking or beam gating are used, a phantom irradiation that includes a moving table to simulate respiratory movement must be used for credentialing. This step fulfills the requirement for motion management. For institutions not using either gating or tracking, completing the Facility Questionnaire by describing the motion management technique completes this requirement.
- Third, institutions intending to use 3D-CRT only as their as their planning and delivery technique when entering patients on this protocol also will have to complete the Benchmark credentialing test discussed in the IMRT section 5.2.2, above, using 3D-CRT. The details of the Benchmark credentialing are described in Section 5.4. The Benchmark case is available online on the IROC Houston web site, http://irochouston.mdanderson.org; select "Credentialing" and "RTOG". RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study.
- Fourth, institutions are required to send planning contouring information for the initial patients they register for treatment on this study for Pre-treatment Review before the start of RT. This Pre-treatment Review process is described further in Sections 5.2.2 and 5.4.

5.4 The Benchmark, Rapid Review, and Image Registration Credentialing Process (2/25/14)

5.4.1 Benchmark Credentialing

The credentialing process consists of a Benchmark test case provided by the Study Chairs of this protocol, as described in Section 5.2.2 for IMRT and in Section 5.3.2 for 3D-CRT. The Benchmark case is available at http://irochouston.mdanderson.org; select "Credentialing" and "RTOG".

The purpose of the Benchmark credentialing case planned per Arm 2 requirements is to:

1) verify the institution's ability to submit treatment planning and imaging data using an appropriate digital format;
2) demonstrate the institution's understanding and implementation of details of this protocol;
3) verify the institution's ability to correctly contour structures and targets;
4) confirm the institution's ability to produce treatment plans that meet the requirements of the protocol, which include accurate image registration.

Case, imaging, and procedural instructions related to the Benchmark credentialing can be directly downloaded from http://irochouston.mdanderson.org; select "Credentialing" and "RTOG".. This protocol should be used as the instruction for target delineation and RT adaptive planning. **The Benchmark should be submitted for review according to Section 12.** The credentialing criteria of the Benchmark are the same as specified in this protocol for actual cases with minor deviation, as specified in Section 6.0.

5.4.2 Image Registration Credentialing

Image Registration credentialing is in addition to the requirement for daily IGRT for patient positioning on the RT treatment couch. This requirement addresses the registration of the pre- and during-RT PET/CT with the CT-simulation study performed at the start of treatment. The credentialing of the imaging registration will be performed as part of the credentialing Benchmark case. Detailed instructions are available online. The institution must submit the screen captures of the registrations of CT1/PET1, CT2/PET2, CT1/CT2 with axial, sagittal, and coronal views through the center of the target volume as specified in Section 12.2. Imaging registrations will be further reviewed by the Study Chairs during the real Pre-Treatment Review for the initial cases from each center.

5.4.3 Pre-Treatment Reviews

Pre-treatment review credentialing of the initial patients is designed to further verify an institution's ability to correctly contour structures and create protocol compliant treatment plans. Like the Benchmark credentialing procedure, pre-treatment reviews can further verify the institution's ability to adhere to the protocol instructions. The idea of the pre-treatment review process is to require institutions to send their radiation treatment plan for the first patient that is randomized to the "adaptive" arm (Arm 2) for pre-treatment review by the Study Chairs. This patient cannot start treatment until the pre-treatment review is completed and approval received from IROC Philadelphia-RT (former RT Quality Assurance (RTQA). Subsequent patients may not be enrolled until the pre-treatment review is approved and the site is notified by IROC Philadelphia-RT.

5.5 Pre-Registration Requirements for FDG-PET and CT Guided Adaptive Radiation Therapy (12/19/13)

5.5.1

Only institutions that have met the following requirements may enter patients onto this study.

- The institution must have an ACRIN qualified PET/CT scanner and must follow ACRIN scanning protocols (see Section 6.14). This scanner must be used on all patients entered onto this trial. The credentialing process and application forms, as well as the FDG-PET standard operating procedures (SOPs) are available on the PET Core Lab web site (browse at http://www.acrin.org/CORELABS/PETCORELABORATORY.aspx). Facilities that have a qualified scanner are listed at http://www.acrin.org/CORELABS/NCICQIEQUALIFICATIONPROGRAM/NCICQIEQUALIFIEDSITES.aspx.

- For this study, the institution must use a flat palette imaging couch for scanning for imaging registration match with simulating CT for both the FDG-PET/CT and FMISO-PET/CT. Accurate imaging registration is essential before enrolling any patient for this protocol.

- Adequate image registration between FDG-PET and the CT from the PET/CT scanner and the CT of the PET/CT with a simulating CT is required. Deformable registration is not permitted.

5.5.2 Scanners qualified within the last 2 years for other ACRIN studies involving quantitative FDG-PET/CT will be automatically credentialed for this study (after verification of the above requirements by the ACRIN PET Core Laboratory and confirmation of a flat palette imaging couch).

5.5.3 Credentialing for imaging registration and target delineation can be accomplished through completion of the credentialing Benchmark study, available at http://irochouston.mdanderson.org; select "Credentialing" and "RTOG".

5.6 Digital RT Data Submission to RTOG Using TRIAD (12/19/13)

TRIAD is the American College of Radiology's (ACR) image exchange application and it is used by the Radiation Therapy Oncology Group (RTOG). TRIAD provides sites participating in RTOG clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to Section 5.0 of the protocol for instructions on how to request a CTEP-IAM account.
- To submit images, the site physics user must have been assigned the 'TRIAD site user' role on the relevant Group or CTSU roster. RTOG users should contact your site Lead RA to be added to your site roster. Users from other cooperative groups should follow their procedures for assignment of roster roles.
- RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:
When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the RTOG website Core Lab tab.

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

5.7 Regulatory Pre-Registration Requirements (2/25/14)

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch (PMB), CTEP, DCTD, NCI. These forms are available on the CTSU registered member web site or by calling the PMB at 240-276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for RTOG 1106 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- CTSU RT Facilities Inventory Form (if applicable)

NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the IROC Houston monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

5.7.1 **In addition to the requirements noted above, ALL** institutions must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, https://www.ctsu.org/public/CTSU-IRBcertif_Final.pdf, prior to registration of the institution's first case:

- IRB/REB approval letter;
- IRB/REB approved consent (English and native language versions*****);
  ***Note**: Institutions must provide certification/verification of IRB/REB consent translation to RTOG Headquarters (described below)
- IRB/REB assurance number

Non-English Speaking Canadian and Non-North American Institutions:
Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved RTOG will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

5.7.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS
Prior to clinical trial commencement, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.

5.7.3 Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS
***For institutions that do not have an approved LOI for this protocol*:**
International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/Researchers/InternationalMembers.aspx .

***For institutions that have an approved LOI for this protocol*:**
All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.8 Patient Registration (9/23/13)

5.8.1 OPEN Registration Instructions
Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. All site staff (RTOG and CTSU Sites) will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' web site https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPPA authorization form (if applicable).

Access requirements for OPEN:

- See Section 5.0 for obtaining a CTEP-IAM account.

- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the RTOG, you must have an equivalent 'Registrar' role on the RTOG roster. Role assignments are handled through the Groups in which you are a member.
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.
- **NOTE**: **If you are enrolling as a non-RTOG member site**: Prior to beginning the enrollment, call the RTOG Randomization desk at 215-574-3191 or 215-574-3192 to obtain an RTOG, non-Lead Group, site-specific institution number.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In the event that the OPEN system is not accessible, participating sites can contact RTOG web support for assistance with web registration: websupport@acr.org or call the RTOG Registration Desk at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

6.0 RADIATION THERAPY/FUNCTIONAL IMAGING (2/25/14)

This trial is not utilizing the services of the ITC for dosimetry digital treatment data submission. See Section 5.2 for information on installing TRIAD for submission of digital RT data prior to enrolling patients.

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, IROC Philadelphia-RT 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 (2/25/14)

<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 36-38 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>
<tr><td>Continue treatment of the initial plan at 2 Gy per fraction without changes or adaptions</td><td>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 6.5.3)</td></tr>
<tr><td>To a total dose of 60 Gy</td><td>To a maximum physical dose or 80.4 Gy (first phase plus adaptive boost)</td></tr>
</table>

6.1 Dose Specifications (2/25/14)

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 CT1PT1PTV, CT1PT1CTV, and PT2PTV 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 IROC Houston (former Radiologic Physics Center [RPC]) web site at http://irochouston.mdanderson.org. Click on the highlighted box in the upper right corner of the web site. Call the IROC Houston 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 (2/25/14)

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
PT1GTV	PT1 Primary and Nodal Metabolic Tumor Volumes	Autotracked at threshold of 1.5 x mean intensity of 1 cc aorta volume	Defined on PT1; Transferred to CT1 for contour review.
CT1PT1GTV	GTV for Arm 1 and Initial Plan of Arm 2	Composite of CT1GTV and PT1GTV	Created on CT1
CT1PT1CTV	CTV for Arm 1 and Initial Plan of Arm 2	0.5 cm expansion from CT1PT1GTV	Created on CT1
CT1PT1PTV	PTV for Arm 1 and Initial Plan of Arm 2	0.5 cm expansion from CT1PT1CTV	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; Must becopied to CT1 for dose evaluation
PT2GTV	PT2 Primary and Nodal Metabolic Tumor Volumes	Autotracked at threshold of 1.5 x mean intensity of 1 cc aorta volume	Defined on PT2; Must be 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)
PT2GTV	Main GTV for Adaptive Plan of Arm 2	Equals PT2GTV	Created on CT1 (note: source PT2GTV on registered PT2 dataset)
PT2PTV	Main PTV for Adaptive Plan of Arm 2	0.5 cm expansion from PT2GTV (note: there is no PT2CTV)	Created on CT1

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

The initial planning target volume (CT1PT1PTV) 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 (PT1). 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 volumes 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/GTV (PT1GTV) 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.

PT1GTV plusCT1GTV makes the total CT1PT1GTV. The initial clinical target volume (CT1PT1CTV) will consist of the CT1PT1GTV 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 CT1PT1CTV. The CT1PT1PTV will consist of the CT1PT1CTV 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 CT1PT1GTV did not include the target motion.

Target Volume for the Arm 2 Adaptive Treatment

The primary PTV for the adaptive plan will be the PT2GTV, which is defined based on the during-RT PET/CT study and consists of the PT2GTV plus at least a 0.5 cm expansion. The PT2GTV should be outlined on the PET/CT scan acquired at fx 18-19 during the course of RT. The PT2GTV 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 PT1GTV.

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 PT2PTV 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 (2/25/14)

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 CT1PT1PTV 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 PT2PTV and meets the normal tissue constraints listed in Table 6.5.3.** 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. **All files must be referenced to CT1 when exporting for RT data submission**. 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: PT1, CT1. PT1 should be used for PT1GTV determination;
c) During-RT FDG-PET-CT: PT2, CT2. PT2 defines PET targets for adaptive plan, while CT2 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 CT2GTV 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 CT2PTV receives the prescribed dose. In addition, the CT2PTV, CT1PT1CTV, and CT1PT1PTV 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 (2/25/14)

Structure Name	Description	Dose covering 95% volume	Variation Acceptable***	Deviation Unacceptable
CT1PT1CTV	CT1PT1GTV+5mm	60 Gy or above	55-60 Gy	<55 Gy
CT1PT1PTV	CT1PT1CTV+5mm	50 Gy or above	45-50 Gy	<45 Gy
CT2PTV	PTV based on CT2GTV	70 Gy or above**	60-70 Gy	<60 Gy
PT2PTV	PT2GTV+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 6.5.3.**

6.5 Critical Structures (2/25/14)

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

6.5.1 Note: All required structures must be labeled for digital RT data submission as listed in the table below. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name as listed.

The following table outlines the naming of the various tumor volumes and critical structures for submission to TRIAD. Note: Sites must use the spacing, underscores, and capitalization exactly as shown below:

	Prior Terminology	Description
ARM 1 and Initial Plan of ARM 2		
CT1GTV	CT1GTV	CT1 Primary and Nodal Gross Tumor Volume
PT1GTV	PET1MTV	PET1 Primary and Nodal Metabolic Tumor Volume
CT1PT1GTV	PreGTV	GTV for Arm 1 and Initial Plan of Arm 2
CT1PT1CTV	PreCTV	CTV for Arm 1 and Initial Plan of Arm 2
CT1PT1PTV	PrePTV	PTV for Arm 1 and Initial Plan of Arm 2
Lungs	Lungs	Lungs minus CT1PT1GTV
Heart	Heart	Heart/Pericardium (please refer to atlas on RTOG website)
Esophagus	Esophagus	Esophagus
SpineCanal	SpinalCord	Spinal Canal
BrachialPlexus	BrachialPlexus	Brachial Plexus
NonPTV	NonPTV	External minus PTV

	Prior Terminology	Description
ARM 2 Adaptive Plan		
CT2GTV	CT2GTV	CT2 Primary and Nodal Gross Tumor Volume; Secondary GTV for Adaptive Plan of Arm 2
PT2GTV	DurGTV= PET2MTV	PET2 Primary and Nodal Metabolic Tumor Volume
CT2PTV	CT2PTV	PTV based on CT2GTV; Secondary PTV for the Adaptive Plan of Arm 2
PT2PTV	DurPTV	Main PTV for Adaptive Plan of Arm 2

6.5.2 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.

6.5.3 Organs at Risk Tolerances

All of the critical organs listed below in Table 6.5.3 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 6.5.3 (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 6.5.3: Dose Limits for Organs at Risk for the Final Composite Plan* (2/25/14)

DICOM Structure Name	Description	Metric	Per Protocol	Variation Acceptable	Deviation Unacceptable
Lungs	Lungs minus CT1PT1GTV	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
SpinalCanal	Spinal Cord	Max Dose (Gy, 0.03 cc)	≤ 50 Gy	>50 Gy but ≤ 52 Gy	> 52 Gy
BrachialPlexus	Brachial Plexus	Max Dose (Gy, 0.03 cc)	≤ 63 Gy	>63 Gy but ≤ 65 Gy	> 65 Gy
NonPTV	External – minus 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 (2/25/14)

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 Table 6.5.3). The minimum dose within the PTV can fall below the 90% stated in Table 6.5.3, but underdosing must be confined to areas near overlap with critical structures listed in Table 6.5.2. Table 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 ventilation	**Radiation fibrosis** causes respiratory insufficiency, requiring assisted 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) throughout 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.

7.0 DRUG THERAPY

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

Protocol treatment must begin within 2 weeks after registration.

7.1 Concurrent Chemotherapy (2/25/14)

Chemotherapy will be administered weekly concurrent with radiation on the same day each week. Carboplatin (AUC 2, IV) and Paclitaxel (45 mg/m^2, IV) will be started on week 1 of thoracic radiotherapy and will be continued weekly for 6 weeks (Note: 7 weeks of chemotherapy is allowed if chemotherapy begins early or if radiation is extended past 6 weeks). Patients may receive chemotherapy on any day of the week from Monday to Friday, but the day of administration should remain constant during the course of chemoradiotherapy. A 1-day shift in the day of weekly chemotherapy infusion will be allowed if necessary. Paclitaxel will be given prior to carboplatin.

Weekly Concurrent Chemotherapy Regimen

Agent	Dose	Route	Infusion Time
Paclitaxel	45 mg/m^2	IV	1 hour
Carboplatin	AUC 2	IV	½ hour

7.1.1 Paclitaxel

Paclitaxel 45 mg/m^2 IV will be given by one hour infusion. Paclitaxel is mixed in non-PVC containers per the usual guidelines of the pharmacy.

7.1.2 Carboplatin

Carboplatin will be given at AUC 2 over 1/2 hour immediately after paclitaxel using the Calvert **formula:**

Calculated dose of carboplatin (mg) = target AUC x (glomerular filtration rate (GFR) + 25) as per the Cockroft-Gault formula or Jelliffe equation):

Cockroft-Gault formula:

$$GFR = \frac{(140 - Age) \times Actual\ Weight\ (in\ kilograms) \times 0.85\ (females\ only)}{72 \times Serum\ Creatinine\ (in\ mg/dL)}$$

Jelliffe equation:
Male: (98 - (0.8 * (age - 20)) / (SCR in mg/dL)) x Patient's BSA/1.73 M2
Female: Multiply above result by 0.9

Maximum carboplatin dose (mg) = target AUC(mg x mg/mL) x 150 mL/min. Therefore, the maximum carboplatin dose should not exceed target AUC (mg x min/mL) x 150 mL/min, but it may be less.

NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

7.1.3 Prior to receiving carboplatin and paclitaxel, all patients should receive standard pre-medication. One standard that is recommended is:

- Dexamethasone 20 mg orally 12 and 6 hours before paclitaxel or 20 mg IV just prior to paclitaxel;
- Diphenhydramine 50 mg IV (or equivalent) prior to paclitaxel;
- Cimetidine 300 mg IV (or equivalent, ranitidine 50 mg or famotidine 20 mg) prior to paclitaxel;
- Granisetron 2 mg orally (or equivalent) prior to chemotherapy

7.2 Consolidation Chemotherapy

Consolidation chemotherapy will start approximately 4-6 weeks after the completion of all radiotherapy when esophagitis and chemotherapy-induced neuropathy are grade 1 or less, and ANC > 1500 and platelet count > 100,000. If the ANC and platelet count are not at the required levels, chemotherapy should be delayed until the following week. Carboplatin (AUC 6, IV) and Paclitaxel (200 mg/m^2, IV) will be given on day 1. This will be repeated every 21 days for a total of 3 cycles, on the same day of the week for each cycle.

Consolidation Chemotherapy Regimen

Agent	Dose	Route	Infusion Time	Days for administration
Paclitaxel	200mg/m^2	IV	3 hours	q 21 days × 3 cycles
Carboplatin	AUC 6	IV	½ hour	q 21 days × 3 cycles

7.3 Paclitaxel (Taxol)

The use of paclitaxel in this protocol meets the criteria described under Title 21 CFR 312.2(b) for IND exemption. See package insert for further details.

7.3.1 Classification and Mode of Action

Paclitaxel is an antimicrotubule agent that promotes microtubule assembly and stabilizes tubulin polymers by preventing their depolarization, resulting in the formation of extremely stable and nonfunctional microtubules, and consequently inhibition of many cell functions

7.3.2 Availability

A concentrated solution of 6 mg/ml in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol 50% is in 5, 16.7, and 50 ml vials.

7.3.3 Storage and Stability

Freezing does not adversely affect the product. Solutions diluted to a concentration of 0.3 to 1.2 mg/ml in normal saline, 5% dextrose, 5% dextrose and normal saline, or 5% dextrose in Ringer's solution are stable for up to 27 hours when stored at room temperature and normal room light.

7.3.4 Preparation

The concentrated solution must be diluted prior to use in normal saline, 5% dextrose, 5% dextrose and normal saline, or 5% dextrose in Ringer's solution to a concentration of 0.3 -1.2 mg/ml. Solutions exhibit a slight haze, common to all products containing non-ionic surfactants. Glass, polypropylene, or polyolefin containers and non-PVC-containing (nitroglycerin) infusion sets should be used. A small number of fibers (within acceptable limits established by the USP) have been observed after dilution. Therefore, a hydrophilic 0.22 micron in-line filter should be used. Analyses of solutions filtered through IVEX-2 and IVEX-HP (Abbott) 0.2 micron filters showed no appreciable loss of potency. Solutions exhibiting excessive particulate formation should not be used.

7.3.5 Administration

Concurrent Chemotherapy: Weekly, 45 mg/m^2, as an intravenous infusion over 1 hour.

Consolidation Chemotherapy: Every 21 days x 3 cycles, 200mg/m^2, as an intravenous infusion over 3 hours.

7.3.6 Incompatibilities

Avoid the use of PVC bags and infusion sets due to leaching of DEHP (plasticizer). Prior administration of cisplatin may increase myelosuppression because of reduced clearance of paclitaxel. Ketoconazole, verapamil, diltiazem, quinidine, dexamethasone, teniposide, etoposide, vincristine, and cyclosporine may inhibit paclitaxel metabolism, based on in vitro data.

7.3.7 Anticipated Adverse Events

- *Hematologic*: Myelosuppression (neutropenia, leukopenia, thrombocytopenia, anemia);
- *Hypersensitivity*: Thought to be caused by the Cremophor vehicle; minor symptoms include hypotension, flushing, chest pain, abdominal r extremity pain, skin reactions, pruritus, dyspnea, and tachycardia; more severe reactions include hypotension requiring treatment, dyspnea with bronchospasm, generalized urticaria, and angioedema. The majority (53%) of the reported reactions occurred within 2-3 minutes of initiation of treatment and 78% occurred within the first 10 minutes. Reactions usually occurred with the first and second doses.
- *Cardiovascular*: Atrial arrhythmia (sinus bradycardia [usually transient and asymptomatic], sinus tachycardia, and premature beats); significant events include syncope, hypotension, other rhythm abnormalities (including ventricular tachycardia, bigeminy, and complete heart block requiring

pacemaker placement), and myocardial infarction. Hypertension (possibly related to concomitant medication --Dexamethasone) may also occur.

- *Neurologic*: Sensory (taste changes); peripheral neuropathy; arthralgia and myalgia (dose-related, more common when colony-stimulating factors are also administered); seizures; mood alterations; neuroencephalopathy; hepatic encephalopathy; motor neuropathy; and autonomic neuropathy (paralytic ileus and symptomatic hypotension).
- *Dermatologic*: Alopecia (universal, complete and often sudden, between days 14-21); injection site reactions (erythema, induration, tenderness, skin discoloration); infiltration (phlebitis, cellulitis, ulceration, and necrosis, rare); radiation recall; and rash.
- *Gastrointestinal*: Nausea, vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis (neutropenic enterocolitis), ischemic colitis, and pancreatitis.
- *Hepatic*: Increased AST, ALT, bilirubin, alkaline phosphatase; hepatic failure, and hepatic necrosis.
- *Other*: Fatigue, headache, light-headedness, myopathy, elevated serum creatinine, elevated serum triglycerides, and visual abnormalities (sensation of flashing lights, blurred vision).

7.3.8 Supply

Commercially available

7.4 Carboplatin (8/19/13)

The use of carboplatin in this protocol meets the criteria described under Title 21 CFR 312.2(b) for IND exemption. See package insert for further details.

7.4.1 Classification and Mode of Action

Second generation tetravalent organic platinum compound. Like cisplatin, carboplatin produces predominantly interstrand DNA crosslinks rather than DNA-protein crosslinks. Cell-cycle nonspecific.

7.4.2 Availability

Available in 50, 150, and 450 mg vials.

7.4.3 Storage and Stability

Store the unopened vials at controlled room temperature 15° - 30°C (59°-86°F). Protect unopened vials from light. Solutions for infusion should be discarded 8 hours after preparation.

7.4.4 Preparation

Add 5, 15, or 45 ml sterile water, normal saline, or 5% dextrose to the 50, 150, or 450 mg vial, respectively. The resulting solution contains 10 mg/ml. The desired dose is further diluted, usually in 5% dextrose.

7.4.5 Administration

Concurrent Chemotherapy: Weekly, AUC 2 as an intravenous infusion over 1/2 hour.

Consolidation Chemotherapy: Every 21 days x 3 cycles, AUC 6 as an intravenous infusion over 1/2 hour.

7.4.6 Incompatibilities

General: Needles or intravenous administration sets containing aluminum parts that may come in contact with paraplatin should not be used for the preparation or administration of the drug. Aluminum can react with carboplatin causing precipitate formation and loss of potency.

7.4.7 Compatibilities

Carboplatin (0.3 mg/ml) is chemically compatible in normal saline or 5% dextrose for 24 hours at room temperature.

7.4.8 Anticipated Adverse Events

- *Hematologic*: Thrombocytopenia, neutropenia, leukopenia, more pronounced in patients with compromised renal function and heavily pretreated patients; may be cumulative.
- *Gastrointestinal*: Nausea and vomiting (less severe than with cisplatin), treatable with moderate doses of antiemetics.
- *Dermatologic*: Rash, urticaria.
- *Hepatic*: Abnormal liver function tests, usually reversible with standard doses.
- *Neurologic*: Rarely peripheral neuropathy.
- *Renal:* Elevations in serum creatinine, BUN; electrolyte loss (Na, Mg, K, Ca).
- *Other*: Pain, asthenia.

7.4.9 Supply

Commercially available.

7.5 Accountability

Drug accountability records must be maintained at all sites according to good clinical practices and NCI guidelines.

7.6 Dose Modifications

7.6.1 If treatment is interrupted due to a non-dose-limiting adverse event or any reason other than toxicity, such as a holiday, bad weather, or a transportation problem, the duration of therapy will be extended accordingly. If a patient misses a day of radiation and chemotherapy, then the weekly chemotherapy should be delivered the next day and the missed radiation fraction will be given after the completion of planned treatments.

7.6.2 Patients who exhibit distant tumor progression will discontinue all study procedures and will be medically managed. These patients will continue to be followed as specified in the protocol. These patients may be treated with other agents. Patients who exhibit local-regional tumor progression will complete radiation as described in Section 6.0. Tissue confirmation is highly recommended to confirm the progressive disease.

7.6.3 Dose Levels

Patients will be treated at the following dose levels

Dose Levels of Paclitaxel and Carboplatin

	Starting Dose	Dose Level -1	Dose Level -2
Concurrent Therapy[a]			
Paclitaxel	45 mg/m^2	NA	NA
Carboplatin	AUC=2	NA	NA
Consolidation Therapy[b]			
Paclitaxel	200 mg/m^2	150 mg/m^2	NA
Carboplatin	AUC=6	AUC=4.5	NA

[a] For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.

[b] For consolidation therapy, dose reductions of paclitaxel and carboplatin below the -1 dose level will not be allowed.

7.6.4 Paclitaxel/Carboplatin Dose Modifications for Hematologic Toxicity During Concurrent Therapy

Toxicity CTCAE Grade (CTCAE, v. 4)	**Paclitaxel Dose At Start of Subsequent Cycles of Therapy** [a]	**Carboplatin Dose at Start of Subsequent Cycles of Therapy** [a]
Neutrophil count decreased (Neutropenia)		
1 <LLN - 1500/mm^3; <LLN - 1.5 x 10e9 /L	Maintain dose level	Maintain dose level
2 <1500 - 1000/mm^3; <1.5 - 1.0 x 10e9 /L	Maintain dose level	Maintain dose level
3 <1000 - 500/mm^3; <1.0 - 0.5 x 10e9 /L	Hold therapy[b]	Hold therapy[b]

4 <500/mm^3; <0.5 x 10e9 /L	Hold therapy[b]	Hold therapy[b]
Febrile neutropenia (Neutropenic fever)	Hold therapy[b]	Hold therapy[b]
Platelet count decreased (Thrombocytopenia)		
1 <LLN - 75,000/mm^3; <LLN - 75.0 x 10e9 /L	Maintain dose level	Maintain dose level
2 <75,000 - 50,000/mm^3; <75.0 - 50.0 x 10e9 /L	Hold therapy[b]	Hold therapy[b]
3 <50,000 - 25,000/mm^3; <50.0 - 25.0 x 10e9 /L	Hold therapy[b]	Hold therapy[b]
4 <25,000/mm^3; <25.0 x 10e9 /L	Hold therapy[b]	Hold therapy[b]
Other Hematologic toxicities	There will be no dose modifications for changes in white blood cell counts (leukopenia) or lymphocyte count decreased (lymphopenia).	

a. Dose levels are relative to the starting dose in the previous cycle. For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.
b. Repeat lab work weekly and resume chemotherapy based on this table.

- Doses that are missed during weekly schedule concurrent with radiation will not be made up but will be documented.

- Radiation therapy will be held for grade 4 hematologic toxicities described in the table above.

7.6.5 If paclitaxel and/or carboplatin doses must be withheld for greater than two consecutive weeks, the drug(s) will be held permanently for the duration of concurrent therapy.

7.6.6 Paclitaxel/Carboplatin Dose Modifications for Non-Hematologic Toxicity During Concurrent Therapy

Worst Toxicity CTCAE Grade (CTCAE, v. 4) [a, c]	**Paclitaxel Dose At Start of Subsequent Cycles of Therapy**[b]	**Carboplatin Dose At Start of Subsequent Cycles of Therapy**[b]
Neuropathy (peripheral sensory)		
≤ Grade 1	Maintain dose level	Maintain dose level
Grade 2	Hold therapy until Grade ≤ 1; restart at full dose	Maintain dose level
Grade 3	Discontinue therapy	Maintain dose level
Other non-hematologic toxicities		
≥ Grade 3	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2

a. For ≤ CTCAE Grade 2 non-hematologic toxicity not described above, excluding neuropathy, maintain dose level of all study. For neuropathy, follow the guidelines listed above.
b. Dose levels are relative to the starting dose in the previous cycle. For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.
c. Radiation therapy should continue to be delivered for ≤ Grade 3 non-hematologic toxicities in or outside the radiation treatment field. RT should be held for all Grade 4 non-

hematologic toxicity in or outside the treatment field and resumed only when toxicity is ≤ Grade 2.

7.6.7 Carboplatin Dose Modifications for Renal Toxicity

A > 10% change in the serum creatinine, based on weekly calculated creatinine clearance, will warrant a recalculation of the carboplatin dose (see Section 7.6.4)

7.6.8 Paclitaxel for Neuropathy

If paclitaxel doses must be withheld for greater than two consecutive weeks, the drug will be held permanently for the duration of concurrent therapy (see Section 7.6.6).

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. Re-evaluate patient after one week for resumption of radiotherapy.

7.6.9 Paclitaxel/Carboplatin/RT Dose Modifications for In RT Field, Non-Hematologic Toxicity During Concurrent Therapy

Treatment Modification for In-field Non-Hematologic Toxicity				
In-field	**CTCAE, v. 4 Toxicity Grade**	**XRT**	**Paclitaxel**	**Carboplatin**
Esophagus/pharynx *(on day of XRT)*	4	Hold treatment until ≤ Grade 2; evaluate at least weekly	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Esophagus/pharynx *(on day of chemo)*	3	No change or hold ≤ 5 days (See Sections 7.6.12 and 7.6.13)	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Esophagus/pharynx *(on day of chemo)*	2	No change	No change	No change
Pulmonary	4	Discontinue	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Pulmonary	3	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Skin	4	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Skin	3	No change	No change	No change

7.6.10 For dermatitis or other in-field, radiotherapy-related toxicity, see the table in Section 7.6.10. On day of chemotherapy administration during any treatment week, omit paclitaxel and carboplatin until toxicity resolves to grade ≤ 2 as detailed in the table above.

7.6.11 Radiotherapy should be interrupted for grade 4 esophagitis, discontinued for grade 4 pulmonary toxicity, and resumed according to the table in Section 7.6.10. If treatment is interrupted for > 2 weeks, protocol treatment should be discontinued. Follow up and data collection will continue as

specified in the protocol. Further treatment off protocol is at the discretion of the treating physician. If the patient experiences esophagitis so that *IV* fluid support is needed, insertion of a feeding tube should be considered.

7.6.12 For Grade ≥ 3 esophagitis/pharyngitis, dermatitis, or other in-field, radiotherapy-related toxicity, on day of chemotherapy administration during any treatment week, omit paclitaxel and carboplatin until toxicity resolves to grade ≤ 2 as detailed in the table above.

7.6.13 For Grade 3 esophagitis, radiotherapy can be continued with pain management and IV support, or radiotherapy can be held for ≤ 5 days until symptoms are < Grade 3.

7.6.14 Paclitaxel/Carboplatin Dose Modifications for Hematologic Toxicity During Consolidation Therapy

Toxicity CTCAE Grade (CTCAE, v. 4)	**Paclitaxel Dose At Start of Subsequent Cycles of Therapy** [a, c]	**Carboplatin Dose at Start of Subsequent Cycles of Therapy** [a, c]
Neutrophil count decreased (Neutropenia)		
1 <LLN - 1500/mm^3; <LLN - 1.5 x 10e9 /L	Maintain dose level	Maintain dose level
2 <1500 - 1000/mm^3; <1.5 - 1.0 x 10e9 /L	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 mm^3
3 <1000 - 500/mm^3; <1.0 - 0.5 x 10e9 /L	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 mm^3
4 <500/mm^3; <0.5 x 10e9 /L	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3
Febrile neutropenia (Neutropenic fever)	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3
Platelet count decreased (Thrombocytopenia)		
1 <LLN - 75,000/mm^3; <LLN - 75.0 x 10e9 /L	Maintain dose level	Maintain dose level
2 <75,000 - 50,000/mm^3; <75.0 - 50.0 x 10e9 /L	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3
3 <50,000 - 25,000/mm^3; <50.0 - 25.0 x 10e9 /L	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3
4 <25,000/mm^3; <25.0 x 10e9 /L	Hold therapy[b] and decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 75,000 mm^3
Other Hematologic toxicities	There will be no dose modifications for changes in white blood cell counts (leukopenia) or lymphocyte count decreased (lymphopenia).	

a. Dose levels are relative to the worst toxicities in the previous cycle. For consolidation therapy, dose reductions of paclitaxel and carboplatin below the –1 dose level will not be allowed.
b. Repeat lab work weekly and resume chemotherapy based on this table.
c. Dose delays greater than 2 weeks will warrant discontinuation of chemotherapy for the consolidation cycles.

7.6.15 Paclitaxel/Carboplatin Dose Modifications for Non-Hematologic Toxicity During Consolidation Therapy

Worst Toxicity CTCAE Grade (CTCAE, v. 4) [a]	**Paclitaxel Dose At Start of Subsequent Cycles of Therapy** [b]	**Carboplatin Dose At Start of Subsequent Cycles of Therapy** [b]
Neuropathy (peripheral sensory) See Section 7.6.18 for further details		
≤ Grade 1	Maintain dose level	Maintain dose level
Grade 2	Hold therapy until Grade ≤ 1; restart at full dose	Maintain dose level
Grade 3	Discontinue therapy	Maintain dose level
Other non-hematologic toxicities		
Grade 3	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2

a. For ≤ CTCAE Grade 2 non-hematologic toxicity not described above, maintain dose level of all study drugs.
b. Dose levels are relative to the worst toxicities in the previous cycle.

When a chemotherapy dose reduction is required during the consolidation therapy, re-escalation of the chemotherapy dose will not be allowed for subsequent doses during that specific course.

7.6.16 Carboplatin Dose Modifications for Renal Toxicity

A > 10% change in the serum creatinine, based on weekly calculated creatinine clearance, will warrant a recalculation of the carboplatin dose.

7.6.17 Paclitaxel Dose Modifications for Neuropathy

If paclitaxel doses must be withheld for greater than 2 consecutive weeks, the drug will be held permanently for the duration of consolidation therapy. If protocol treatment is discontinued for any reason, follow up and data collection will continue as specified in the protocol

The reason(s) for discontinuation from protocol treatment should be documented in the patient's medical record and Case Report Form (CRF). All patients should be followed as specified in Sections 11.0, 12.0, and Appendix I.

7.7 Modality Review

The Medical Oncology Co-Chair, Vera Hirsh, MD, will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: **Per Protocol/Acceptable Variation, Not Per Protocol, and Not Evaluable**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

The Medical Oncology Co-Chair, Vera Hirsh, MD, will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. Dr. Hirsh will perform the next review after complete data for the next 20 cases enrolled has been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as

soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.

7.8 Adverse Events (2/25/14)

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event (AE) reporting. The CTCAE version 4.0 is located on the CTEP web site at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

Adverse events (AEs) that meet expedited reporting criteria defined in the table(s) below will be reported via the CTEP-AERS (CTEP Adverse Event Reporting System) application accessed via the CTEP web site (https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613)
In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the RTOG Operations Office at 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

7.8.1 Adverse Events (AEs) (2/25/14)

Definition of an AE: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonization [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. February 29, 2012 http://ctep.cancer.gov/reporting/adeers.html]

7.8.2 Serious Adverse Events (SAEs) (2/25/14)

Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in section 7.9 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in Section 7.9. **Contact the CTEP-AERS Help Desk if assistance is required**.

Definition of an SAE: Any adverse drug event (experience) occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.8.3 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS) (2/25/14)

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis.

Secondary Malignancy:

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)

- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy:
A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

7.9 CTEP-AERS Expedited Reporting Requirements for Chemotherapy/Radiation-Related (non-FMISO) Adverse Events (2/25/14)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the Adverse Event Reporting System, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613.

Submitting a report via CTEP-AERS serves as notification to RTOG and satisfies RTOG requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the RTOG Operations Office at 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

- CTEP-AERS-24 Hour Notification requires that an CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by an CTEP-AERS 5 Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.
- Supporting source document is not mandatory. However, if the CTEP-AERS report indicates in the *Additional Information* section that source documentation will be provided, then it is expected. If supporting source documentation accompanies an CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation **to the RTOG dedicated SAE FAX, 215-717-0990.**
- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS System as “expedited reporting NOT required” must still be reported to fulfill RTOG safety reporting obligations. Sites must bypass the “NOT Required” assessment; the CTEP-AERS System allows submission of all reports regardless of the results of the assessment.

CTEP defines expedited AE reporting requirements for late phase 2 trials as described in the table below. **Important:** All AEs reported via CTEP-AERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

Late Phase 2 and 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies Utilizing Commercially Available Agents within 30 Days of the Last Administration of the Paclitaxel and Carboplatin [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.10 Study Specific Risks/Adverse Event Reporting for FMISO (2/25/14)

Note: For details regarding adverse events and adverse event reporting for the FMISO- PET/CT, see Appendix VI.

Qualifying Adverse Events (AEs), including Serious Adverse Events (SAEs), as defined herein, will be reported via the CTEP-AERS Adverse Event Reporting System (CTEP-AERS) application. All Adverse Events, as defined herein, will, in addition, be reported via CDUS Complete, C3D, or other AE reporting system as specified below.

CTEP-AERS is an electronic, internet based expedited Adverse Event reporting system operated by NCI/CTEP. It is generally used to capture and disseminate information on relatively significant Adverse Events, based upon trial stage, expectedness, severity, and attribution. However, it may be used to report adverse events of all types if CTEP-AERS reporting is required per protocol.

For this study, Adverse Event reporting must follow the guidelines and timing requirements below. The latest version of the NCI/CTEP Adverse Event Reporting Requirements document, which is available at: https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613.

This document provides additional details, and may be consulted as a reference, but does not supersede AE reporting as specified in this protocol.

The electronic-CTEP-AERS AE system is to be used for all 'expedited reporting' events as defined herein. If the system is temporarily unavailable, a paper and telephone/FAX based process is provided herein. If expedited AE data has been submitted via the manual (i.e. telephone/fax) process, it is to be re-submitted via the electronic CTEP-AERS system as soon as is possible.

7.11 General Definitions

Adverse Event (AE): For the purpose of this study, an Adverse Event is an untoward medical condition experienced by a study participant **during the Adverse Event reporting period defined in table below of the protocol**, or by applicable guidance, regulation, or policy. An AE is any unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with participation in the study, **regardless of exposure to an agent or procedure, and regardless of whether it is considered to be caused by the agent, device, or process under investigation.**

If there is thought to be a conflict between the protocol and a regulatory or guidance source, consult the CIP Clinical Trials Branch. If a decision must be made pending final clarification, the stricter requirement should be applied.

Life-Threatening Adverse Event: A life-threatening AE is any adverse event that places the study participant, in the clinical opinion of the investigator, at immediate risk of death.

Serious Adverse Event (SAE): An SAE is defined as any untoward medical occurrence that meets any one of the following criteria:

- Results in death or is life-threatening at the time of the event
- Requires inpatient hospitalization, or prolongs a hospitalization
- Results in a persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in a participant's offspring)
- Requires intervention to prevent any of the above, per the investigator/sponsor

NOTE: Any event that:

- Follows IND agent administration, AND
- Occurs within the Expedited AE reporting period defined in the Reporting Table [See Table 'A' Below], AND
- Meets the definition of a Serious Adverse Event (SAE), as described above

MUST be reported through the CTEP-AERS system

All SAEs are to be followed by the investigator until resolution, stabilization, scientifically and clinically satisfactory explanation as to attribution and etiology, or until subject is lost to follow up.

The CTEP Adverse Event Reporting System (CTEP-AERS): CTEP-AERS is a web-based system created by NCI for electronic submission of expedited AE reports & is to be used in this study.

Investigational Agent: An investigational agent is any agent held under an Investigational New Drug (IND) application. For purposes of this study, FMISO is an investigational agent.

Clinical Data Update System (CDUS/Complete CDUS): CDUS/Complete CDUS is a data collection system used to capture clinical data. Complete CDUS is capable of capturing Adverse Event Data and is being used in this study.

7.12 Adverse Events Reporting Requirements (2/25/14)

Note: For details regarding adverse events and adverse event reporting for the FMISO- PET/CT, see Appendix VI.

The list of AEs (see CAEPR/ASAEL below), and the characteristics of an observed AE will determine whether the event requires expedited (via electronic-CTEP-AERS) reporting in addition to routine reporting. For this study CTEP-AERS reporting will be done electronically (via Complete CDUS) reporting.

NOTE: 24-Hour Notification for CIP IND Trials

The adverse event 24-hour notification requirement provides an early detection system for potential safety problems. Adverse events that must be reported within 24-hours of learning of the event are dependent upon the phase of trial, the agent/intervention (investigational or commercial), whether the event is expected or unexpected, the grade, and attribution. The table and footnotes to the table in this section outline 24-hour notification requirements for AEs in trials utilizing an agent under a CIP IND. Adverse events that fulfill the 24-hour reporting requirement must be reported electronically via CTEP-AERS. To ensure vigilance for AEs that require 24-hour notification, CTEP-AERS is programmed to facilitate complete, timely submission.

7.13 Comprehensive Adverse Events & Potential Risks Lists (CAEPR)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single, complete list of reported and/or potential adverse events (AEs) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with bold and italicized text. **This subset of AEs (the ASAEL) contains events that are considered 'expected' for expedited reporting purposes only.**

Please refer to the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/newadverse_2006.pdf for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information.

Comprehensive Adverse Events and Potential Risks List (CAEPR) for [^{18}F]Fluoromisonidazole, (FMISO, NSC 742836, IND #76,042)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with **bold** and *italicized* text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_adeers for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for [^{18}F]Fluoromisonidazole (FMISO).

Version 1.0, July 1, 2010 [1]

Category (Body System)	Adverse Events[2] with Possible Relationship to [^{18}F]Fluoromisonidazole (CTCAE v4.0 Term)	EXPECTED AEs FOR ADEERS REPORTING Agent Specific Adverse Event List (ASAEL)
	No AEs reported in human studies.	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol, and the agent should be included in the e-mail.

Note: No adverse events have been attributed to PET/CT imaging/diagnostic administration of [^{18}F] Fluoromisonidazole at the levels described in the Investigators Brochure. Therefore, no adverse events are expected as a result of the intravenous (IV) administration of [^{18}F]Fluoromisonidazole for typical PET/CT imaging applications such as tumor hypoxia.

Note: As with many IV administered agents, [^{18}F]Fluoromisonidazole could cause an allergic reaction that could potentially pose a threat to life (anaphylaxis). This has not been observed in limited human exposure to date. Reasonable precautions should be taken, consistent with normal radiologic and clinical facility practice. The patient should be monitored until the PET/CT procedure is completed, and trained personnel and emergency equipment should be available per facility standards.

For purposes of informed consent regarding reasonably foreseeable risks to subjects in trials utilizing [^{18}F]Fluoromisonidazole, the following potential adverse events are considered extremely rare:

- **Injection-related risks that may include infection, or accidental extravasation of the dose that may lead to discomfort, localized pain, or infection.**
- **Risks related to allergic reaction/anaphylaxis that may be life threatening.**

Note: As with all PET imaging agents, [^{18}F]Fluoromisonidazole is a radiopharmaceutical that decays with positron emission. As such, it poses an intrinsic radiation exposure risk. However, when administered in accordance with the Investigator's Brochure as a PET imaging agent, this risk is felt to be extremely small. The organ and total body doses associated with [^{18}F]Fluoromisonidazole PET imaging are comparable to or lower than those associated with other widely used clinical nuclear medicine procedures.

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. (See Section 12.0 for AE reporting requirements.)

7.14 Adverse Event Characteristics (2/25/14)

Expected Adverse Event: An expected AE is an event that is listed in the Investigator's Brochure. However, in assessing an AE for the CTEP Adverse Event Reporting System [CTEP-AERS] reporting requirements, the ASAEL portion of the CAEPR for the agent, should be used to determine 'expectedness.'

Unexpected Adverse Event: An unexpected AE is an event that is NOT listed in the Investigator's Brochure. However, in assessing an AE for the CTEP Adverse Event Reporting System [CTEP-AERS]

reporting requirements, the ASAEL portion of the CAEPR for the agent, should be used to determine 'expectedness.'

Attribution: Attribution is a clinical determination, by the investigator, as to whether an AE is related to a medical treatment or procedure. Attribution categories are:

- Definite: The AE is clearly related to a treatment or procedure
- Probable: The AE is likely related to a treatment or procedure
- Possible: The AE may be related to a treatment or procedure
- Unlikely: The AE is likely unrelated to a treatment or procedure
- Unrelated: The AE is clearly not related to a treatment or procedure

NOTE: Attribution is part of the assessment of an adverse event. Determining that an event is 'unlikely related' or 'unrelated' to a study agent or procedure does NOT make the event unreportable, or disqualify the event as an AE. As defined above, an AE is reportable as specified herein if it occurred:

"during the Adverse Event reporting period defined in the protocol, or by applicable guidance, regulation, or policy."

Grade: Grade denotes the severity of the AE. An AE is graded using the following categories:

- Mild
- Moderate
- Severe
- Life-threatening or disabling
- Fatal

NOTE: Severity is graded on a CTCAE based scale for each CTCAE event. For example, an abnormal hemoglobin value is graded for severity from 1 to 5 [death] based upon where that value falls on the CTCAE scale of abnormal Hemoglobin values. "Severity" is NOT the same as "Seriousness," which is an overall assessment [See SAE above] that determines reporting requirements.

7.15 CTCAE term (AE description and grade)

The descriptions and grading scales found in CTCAE version. 4.0, used by protocol of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. All appropriate clinical areas should have access to a copy of the most current CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site (http://ctep.cancer.gov).]

7.16 Expectedness

AEs can be 'Unexpected' or 'Expected' [see above] for expedited reporting purposes only. 'Expected' AEs (i.e., the ASAEL) are bold and italicized in the CAEPR.

7.17 Expedited Adverse Event Reporting for FMISO Adverse Events (2/25/14)

Expedited AE reporting for this study must use electronic CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP web site https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613. Site personnel will be trained in required AE identification and reporting procedures. These requirements are briefly outlined in the table below.

In the rare event that electronic CTEP-AERS [internet] access is lost, an AE report may be submitted using the following process:

1. Sites should download reporting forms in advance and store them locally for access in the event of internet unavailability. They can be found at: http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_adeers
2. Site chooses Single or Multiple Agent template as appropriate
3. Site completes appropriate sections of the SAE submission form.
   NOTE: For 24-hour notification, site follows up with a faxed SAE submission within 5 business days.

4. Site faxes SAE submission form and any additional information (source documents) necessary for thorough review of the event(s) along with the SAE submission form to 301-897-7402, attention CIP SAE Team. The CIP SAE Reporting Desk may be contacted for assistance with any part of this procedure (Tel. 301-897-7497), and should be contacted to confirm receipt of materials sent during any period of CTEP-AERS unavailability, or to provide guidance with the process as appropriate.
5. Site follows up with an e-mail to CIPSAEReporting@tech-res.com notifying the SAE Team that an SAE form and additional information (if available) has been faxed.
6. **For IND studies:** the submission process is not considered complete until an CTEP-AERS report has been submitted electronically.
7. Once CTEP-AERS access is restored, an AE report submitted by the backup process must be entered electronically into CTEP-AERS by the original submitter at the site.
8. CTEP-AERS will be programmed for automatic electronic distribution of reports to the following individuals:

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational

agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

Nutritional support is recommended for all patients. All supportive therapy for optimal medical **CARE WILL BE GIVEN DURING THE STUDY PERIOD AT THE DISCRETION OF THE ATTENDING PHYSICIAN(S) WITHIN THE** parameters of the protocol and documented on each site's source documents as concomitant medication.

Anticonvulsants, antiemetics and antacids, anticoagulants, antidiarrheals, analgesics, antibiotics, and nutritional supplementation are permitted.

9.1.1 Hematopoietic Growth Factors

WBC growth factors (G-CSF/GM-CSF) will not be permitted during radiation. If a patient receives WBC growth factors during radiation, this constitutes a major protocol violation.

9.2 Non-permitted Supportive Therapy

Alternative medical treatments such as herbal products are not allowed during and within 1 year from the initiation of chemoradiation.

10.0 TISSUE/SPECIMEN SUBMISSION

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as specimen submission. Sites are <u>not</u> permitted to delete the specimen component from the protocol or from the sample consent.

10.1 Tissue/Blood Submission

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages patients in protocol studies to consent to the banking of their tissue. The RTOG Biospecimen Resource provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

In this study, tissue will be submitted to the RTOG Biospecimen Resource for the purpose of tissue banking (highly recommended but optional) and blood will be submitted for translational research (highly recommended but optional).

Whole blood, plasma, and serum samples will be drawn 2 weeks prior to radiation therapy (RT). In addition, plasma and serum will be drawn at weeks 2 and 4 during RT and at 3 months post-RT (equivalent to 1 month after completion of chemotherapy). Platelet-poor plasma will be obtained for cytokine and proteomic assays; serum samples will be used for metabolomics, cell death assays and other markers as indicated; buffy coat will be used for genomic studies. Plasma TGF-β1 will be measured by molecular specific Enzyme Linked Immune Sandwich Assay (ELISA). The levels of plasma cytokines will be measured by ready to use kits, such as LINCOplex (microsphere-based sandwich immunoassay) for the concentrations of 29 proinflammatory cytokines, including G-CSF, IL-1α, IL-1β, IL-1ra, IL-6, IL-8, IP-10, MCP-1, MIP-1, TGF-α, and TNF-α. RILT will be diagnosed and graded based on CTCAE 4. The plasma proteomes will be compared using a multiplexed quantitative proteomics approach involving

ExacTag labeling, RP-HPLC and LC-ESI-MS/MS. For genomic studies, we will focus our efforts on (but not limited to) gene specific SNPs of TGFβ1, tissue plasminogen activator (tPA) and angiotensin-converting enzyme (ACE), which are associated with radiation-induced thoracic toxicity such as RILT. Genetic variations within functional locus of these genes will be assessed for in each patient by using gene specific PCR technology. Such SNP studies will be performed using polymerase chain reaction (PCR) and allele specific primers. Variance components models will be used to identify the differential protein expression between patients with and without toxicity. Bioinfomatic methodology may be applied for data analysis. Since this is a prospective study, we anticipate advancement in experimental technology and preliminary results. Other techniques and tests also will be applied if they are found to be superior to the ones stated above. Blood markers (cytokine, proteomic and genomics) during early course of treatment will be correlated to clinical outcome in tumor control.

10.2 Specimen Collection for Tissue Banking and Translational Research (8/19/13)

For patients who have consented to participate in the tissue/blood component of the study (See the sample informed consent)

The following must be provided in order for the case to be evaluable for the Biospecimen Resource:

- One H&E stained slide (slide can be a duplicate cut stained H&E; it does not have to be the diagnostic slide)
- A corresponding paraffin-embedded tissue block of the tumor (the block must match the H&E being submitted) or a 2 mm diameter core of tumor tissue, punched from the tissue block containing the tumor with a punch tool and submitted in a plastic tube labeled with the surgical pathology number. **Note:** A kit with the punch, tube, and instructions can be obtained free of charge from the Biospecimen Resource. Block or core must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.
- The submitted material must be from malignant tumor, not necrotic or fibrotic tissue. If the submitted material is reviewed and is not tumor, the site may be assessed a protocol violation.
- A Pathology Report documenting that the submitted block or core contains tumor. The report must include the RTOG protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.
- A Specimen Transmittal (ST) Form clearly stating that tissue is being submitted for the RTOG Biospecimen Resource; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient's case number.
- The following materials must be provided to the RTOG Biospecimen Resource: A Specimen Transmittal (ST) Form documenting the date of collection of the biospecimen; the RTOG protocol number, the patient's case number, time point of study, and method of storage, for example, stored at -80° C, must be included.

10.2.1 Storage Conditions

Store frozen specimens at -80° C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

Please indicate on the ST Form the storage conditions used and time stored.

10.3 Specimen Collection Summary (2/25/14)

Specimens for Tissue Banking/Translational Research			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
Representative H&E stained slides of the primary tumor	Pre-treatment	H&E stained slide Pre-treatment	Slide shipped ambient
A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or a 2 mm diameter core of tissue, punched from the tissue block with a punch tool	Pre-treatment	Paraffin-embedded tissue block or punch biopsy (must match the H&E slide being submitted)	Block or punch shipped ambient
SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge	2 wks prior to RT (pre-tx), at weeks 2 and 4 during RT, at 3 months post-RT (1 mo. after completion of chemotherapy)	Frozen serum samples containing 0.5 mL per aliquot in 1 mL cryovials (five to ten)	Serum sent frozen on dry ice via overnight carrier
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/ lavender top) and centrifuge for 30 minutes at 4°C	2 wks prior to RT (pre-tx), at weeks 2 and 4 during RT, at 3 months post-RT (1 mo. after completion of chemotherapy)	Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials (five to ten)	Plasma sent frozen on dry ice via overnight carrier
DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/ lavender top) and mix	2 wks prior to RT (if the site missed this collection time point, the site may collect whole blood at any other time or in follow up, but must note this on the ST.	Frozen whole blood samples containing 1 mL per aliquot in 1mL cryovials (three to five)	Whole blood sent frozen on dry ice via overnight carrier

10.3.1 Submit materials for tissue banking and translational research as follows: **(4/10/12)**

U. S. Postal Service Mailing Address: Only for non-urgent, ambient specimens: FFPEs, slides, blocks
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
(2340 Sutter Street, Room S341)
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For all Frozen, Overnight, or Trackable Shipments
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

Questions: 415-476-7864/FAX 415-476-5271; RTOG@ucsf.edu

10.4 Reimbursement

RTOG will reimburse institutions for submission of protocol specified biospecimen materials sent to the Biospecimen Resource at the University of California San Francisco and other protocol-specified collection repositories/laboratories. After confirmation from the RTOG Biospecimen Resource or other designated repository/laboratory that appropriate materials have been received, RTOG Clinical Trials Administration will authorize payment according to the schedule posted with the Reimbursement and Case Credit Schedule found on the RTOG web site (http://www.rtog.org/LinkClick.aspx?fileticket=Csxzt1v1hEk%3d&tabid=323). Biospecimen payments will be processed quarterly and will appear on the institution's summary report with the institution's regular case reimbursement.

10.5 Confidentiality/Storage

(See the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx for further details.)

10.5.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The RTOG Biospecimen Resource database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.5.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for central review will be retained until the study is terminated. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

See Appendix I.

11.1.1 Pre-Treatment Evaluations: Details **(8/19/13)**

- Tumor measurement will be done based on the FDG-PET/CT scan for staging and RT plan. See Section 6.15 for further details of the FDG-PET/CT scan.
- The CT scan or sim CT of chest and upper abdomen should be done with IV contrast.
- The CT scan with contrast of the brain or MRI of the brain is required for all patients.
- Pulmonary function tests include routine spirometry, lung volumes, diffusion capacity, and carbon monoxide (DLCO) are required.
- For patients who are clearly nonresectable, the case can be reviewed by a tumor board with a surgeon or pulmonologist present in lieu of the thoracic surgeon's evaluation.
- A baseline FMISO-PET/CT will be performed on a subset of patients at institutions with access to the radiopharmaceutical that agree to participate in this imaging component. If the site opts to participate, all patients enrolled by the site must receive the FMISO-PET/CT. This scan must be done on a different day from the FDG-PET/CT scan. See Sections 6.12-6.14 for further details of FMISO.
- Electrolytes include a complete panel.

11.1.2 During Treatment Evaluations: Details**8/19/13)**

- *For institutions participating in the FMISO imaging component*: [^{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. See Sections 7.9 and 7.12 and Appendix VI for further details of adverse event reporting.
- For both arms, the FDG-PET/CT scan will be repeated during concurrent radiation and chemotherapy after fraction ~ 18-19 (weeks 3-4).
- Liver function tests (weekly during RT/chemo) include total bilirubin and AST or ALT.
- Electrolytes (weekly during RT/chemo) include a complete panel.

11.1.3 Follow-up Evaluations: Details **(8/19/13)**

- A CT scan of the chest and upper abdomen will be done every 3 months (+/- 2 weeks) during the first year and every 6 months (+/- 2 weeks) during the second year; a chest x-ray is not necessary when a CT scan is done. A contrast-enhanced CT is preferred for the CT scan of chest and upper abdomen. **Note**: For patients who exhibit local-regional tumor progression or distant tumor progression (based on site reporting), CT scans should be done in follow up according to the timeframes above.
- For patients who had initial endobronchial disease, a single bronchoscopy will be performed as clinically indicated between 3 and 4 months after completion of RT or 1 month after the last cycle of consolidation chemotherapy. If a patient experiences severe toxicity and returns for clinical evaluation at a time not designated in Appendix I, blood for research should be drawn (if the patient has consented to participate in the specimen component of the study).
- Timing of follow up: From 1 month to 12 months: +/- 2 week window. For 18-60 months: +/- 1 month window.
- FDG-PET/CT will be performed as clinically indicated between 3 and 4 months after completion of RT or 1 month after the last cycle of consolidation chemotherapy and when CT evidence indicates tumor progression.
- PFTs including DLCO will be performed as clinically indicated between 3 and 4 months after completion of RT or 1 month after the last cycle of consolidation chemotherapy and at 1 year after completion of RT.

11.2 Measurement of Response

11.2.1 PET Scan Criteria

Tumor metabolic response will be evaluated during treatment for all patients; it will not be assessed for post-treatment scans. FDG-PET/CT acquired during standard care (Arm 1) will be used to help CT response assessment.

11.2.2 Tumor metabolic response of irradiated tumor target lesions will be scored by EORTC criteria and by the University of Michigan system (Kong 2007); see Table 11.2.2 below.

Table 11.2.2

	EORTC Criteria (1999)	Michigan Criteria (2007)
CMR	Complete resolution of FDG uptake within the tumour volume so that it was indistinguishable from surrounding normal tissue	Tumor FDG activity decreased to less than the background of the aortic arch blood pool
PMR	Reduction of a minimum of 15±25% in tumour FDG SUV after one cycle of chemotherapy, and greater than 25% after more than one treatment cycle	At least a 30% decrease in the peak of normalized tumor FDG activity of target lesions

SMD	Increase in tumour FDG SUV of <25% or a decrease of <15% and no visible increase in extent of FDG tumour uptake (20%in the longest dimension).	Neither sufficient reduction to qualify for PMR nor sufficient increase to qualify for PMD
PMD	Increase in FDG tumour SUV of >25% within the tumour region defined on the baseline scan, visible increase in the extent of FDG tumour uptake (20% in the longest dimension) or the appearance of new FDG uptake in metastatic lesions	At least a 20% increase in the maximum value of normalized tumor FDG activity of target lesions

11.2.3 The definition of local regional progression has been defined in Section 1.8.3. based on CT criteria (RECIST 1.1), which also takes into consideration the findings of clinical FDG-PET/CT. Local-regional progression will be assessed by the ACRIN core laboratory at 2 years for all patients, at the time of local regional progression, or the time of death if those patients die or relapse earlier than 2 years.

11.3 Criteria for Discontinuation of Protocol Treatment (12/5/12)

In the absence of treatment delays due to adverse events, treatment may continue through completion of concurrent chemoradiotherapy and consolidation chemotherapy or until one of the following criteria applies:

- Distant disease progression;
- Intercurrent illness that prevents further administration of treatment;
- Unacceptable adverse events(s);
- Patient decides to withdraw from the study;
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Patients who become pregnant while on study will be advised according to the investigator or institution's standard process

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

12.0 DATA COLLECTION

Data should be submitted to:

RTOG Headquarters*
1818 Market Street, Suite 1600
Philadelphia, PA 19103

***If a data form is available for web entry, it must be submitted electronically.**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (12/5/12)

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)**	2 weeks after registration
Radiotherapy Form **(T1)** Complete Daily Treatment Record –copy of the RT treatment chart **(T5)**	Within 1 week of end of RT
Concurrent Treatment Form **(TF)**	1 week after the completion of concurrent treatment
Mid-Course PET/CT Form **(FS)**	Within 1 week of completing the mid-course PET/CT scan
Consolidation Treatment Form **(SF)**	1 week after the completion of consolidation treatment
Follow-up Form **(F1)**	At 1 month after the end of treatment, then every 3 months for the first year, every 6 months for years 2-3, then annually

The following forms will be submitted to ACRIN for each FDG-PET/CT scan completed:

Item	Due
FDG PET/CT Technical Assessment Form **(TA)**	Within 2 weeks of scan date
FDG PET/CT Imaging-Related Drug History **(TD)**	Within 2 weeks of scan date
FDG Administration Treatment Exposure Form **(EX)**	Within 2 weeks of scan date
Image Transmittal Worksheet **(ITW)**	Within 2 weeks of scan date*

The TA, TD, and EX forms can be submitted through the ACRIN data center (www.acrin.org).

* The Image Transmittal Worksheet (ITW) must be submitted along with the images for all follow-up CT's done within 2 years (see section 11.2.3), as well as for the baseline and during treatment FDG-PET/CT.

- 3 month follow-up
- 6 month follow-up
- 9 month follow-up
- 12 month follow-up
- 18 month follow-up
- 24 month follow-up

A completed, signed Image Transmittal Worksheet (ITW) MUST be submitted to ACRIN for each time-point. The Image Transmittal worksheet can be found on the ACRIN web site for this study under Protocol Summary Table at http://www.acrin.org/6697_protocol.aspx. The completed ITW can be faxed to (215) 923-1737.

12.2 Summary of Dosimetry Digital Data Submission (Submit to TRIAD; see Section 5.0 for account access and installation instructions) (2/25/14)

Item	Due
Preliminary Dosimetry Information (DD) Digital Data Submission – Treatment Planning Data submitted to RTOG via TRIAD account exported from treatment planning system. **Digital data must be submitted in DICOM format; see Section 5.6 for TRIAD installation details. Note that all structures must be labeled exactly as listed in Section 6.5.1 or resubmission may be required, possibly delaying the review process**	
Arm 1: RT Planning Data • CT1 Dataset (doses and structures linked to this CT) • Contrast CT dataset, if used to aid in target delineation • PET1 (FDG) and PET2 (FDG) datasets (PET2 dataset should be submitted within 1 week of scan) • RT Plan File • RT Dose File • RT Structure File (including all required structures, labeled as described in Section 6.5.1 • JPG screen capture of CT1/PET2 fusion with axial, sagittal, coronal view through the center of the target volume	Within 1 week of start of RT
• RTOG 1106 Datasheet (available at http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1106) • Digital Data Submission Information Form **(DDSI)** – Submitted online http://www.rtog.org/CoreLab/RTQASubmissionInformation.aspx	Within 1 week of scan dates
Note: For F-MISO- PET/CT submissions, see Appendix V for instructions	
Arm 2: Initial Planning Data • CT1 dataset (doses and structures linked to this CT) • Contrast CT dataset, if used to aid in target delineation • PET1 (FDG) dataset • RT Plan File • RT Dose File (Initial) • RT Structure File (including all required structures, labeled as described in Section 6.5.1 • JPG screen capture of CT1/PET1 fusion with axial, sagittal, coronal views through the center of the target volume RTOG 1106 Datasheet (available at http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1106) Digital Data Submission Information Form **(DDSI)** – Submitted online http://www.rtog.org/CoreLab/RTQASubmissionInformation.aspx	Within 1 week of start of RT or, prior to start of RT if pre-treatment review is required **Note: For Pre-Treatment Review cases (1st case from each institution), Initial Planning Data must be submitted, reviewed, and approved prior to the start of initial RT. See Section 6.0 for further details**

Arm 2: Adaptive Planning Data Treatment Plan includes the following in DICOM format: • Primary CT1 dataset(doses and structures linked to this CT) • Adaptive CT2 dataset • Adaptive Contrast CT dataset, if used to aid in target delineation • PET2 (FDG) dataset • RT Plan File (Adaptive and Composite) • (2) RT Dose Files (Adaptive and Composite of initial + adaptive dose files)) • RT Structure File (including all required structures, labeled as described in Section 6.5.1 • JPG screen capture of CT1/PET2 fusion with axial, sagittal, coronal view through the center of the target volume • JPG screen capture of CT1/CT2 fusion with axial, sagittal, coronal view through the center of the target volume • ***Updated*** RTOG 1106 Datasheet (available at http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1106) Digital Data Submission Information Form **(DDSI)** – Submitted online http://www.rtog.org/CoreLab/RTQASubmissionInformation.aspx **Note: For F-MISO- PET/CT submissions, see Appendix V for instructions**	Within 1 week of start of Adaptive RT or, prior to start of Adaptive RT if pre-treatment review is required **Note: For Pre-Treatment Review cases (1st case from each institution), Adaptive Planning Data must be submitted, reviewed, and approved prior to the start of adaptive RT See Section 6.0 for further details.**
Final Dosimetry Information Radiotherapy Form **(T1)** Daily Treatment Record – copy of RT treatment chart **(T5)**	Within 1 week of end of RT

12.3 Summary of Form Data Submission for Sites with Patients Participating in FMISO-PET/CT Imaging

Note: **See Appendix V for details of FMISO-PET/CT imaging submission.**

12.3.1 General

All ACRIN data forms will be entered through ACRIN's Data Center. The web address is www.acrin.org.

12.3.2 Clinical Data Submission

- Upon successful registration to RTOG of participants consented to the FMISO-PET/CT, an ACRIN case-specific calendar will be generated. This calendar lists all forms and designated reports required by protocol along with form due dates at ACRIN's Data Management Center (DMC). The calendars are available 24 hours a day on the ACRIN web site and will be updated as the study proceeds to reflect data that have been received, due dates for queries about unclear data, deadlines for follow-up reports of adverse events, or changes in the protocol that change the data being collected or the timeframe. The research associate may use the calendar as a case management tool for data submission and follow-up scheduling. The investigative site is required to submit data according to protocol as detailed on each participant's ACRIN calendar.
- The user selects the link to the appropriate form and enters data directly into the web-based form. As information is entered into the web form application, various logic checks will be performed. These logic checks look for data that are missing, out of range, or in the wrong format (e.g. character data in a field requiring numeric responses). Such errors will be detected as soon as the user attempts to either submit the form or move to the next data element. The user will not be able to finalize form transmission to the DMC until all data entered pass these logic checks. Forms that are not completed in one sitting can still be submitted and completed at a later date. The form will remain available on the web until the "Complete Form" button is depressed.
- Once data entry of a form is complete, and the summary form is reviewed for completeness and accuracy, the investigator or the research staff presses the "Complete Form" button on the form summary screen and the data is transferred into the clinical database. No further direct revision

of the submitted data is allowed after this point. E-mail confirmation of web data entry is automatically generated and sent to the site investigator or research associate listing all of the data generated and just submitted. Should a problem occur during transmission and the e-mail confirmation of data submission is not received, the investigator or research associate should contact the DMC for resolution of the submission.

- If technical problems prevent access to the Data Center web site, sites will be unable to enter data. The site RA or investigator should notify the DMC if a problem with the Data Center is encountered. All sites will be notified through an ACRIN broadcast message when access to the web data entry is unavailable and the estimated time when access will be restored.. The investigative site should wait until access is restored to submit data.

12.3.3 Data Security

The registration and data collection system has a built-in security feature that encrypts all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system is controlled by a sequence of identification codes and passwords.

12.3.4 Electronic Data Management

Data received from the web-based forms are electronically stamped with the date and time of receipt by the ACRIN server; the data are then entered into the database. A protocol-specific validation program is used to perform more extensive data checks for accuracy and completeness. Complementary validation programs are initiated at the Biostatistics and Data Management Center (BDMC) that are more comprehensive than those built into the web-based data entry screens. The BDMC will run thorough cross-form validations, frequency distributions to look for unexpected patterns in data, and other summaries needed for study monitoring. The validation program generates a log of errors which is managed by the DMC Data Manager (DM). The program is frequently updated to incorporate exceptions to rules so that subsequent validity checks minimize the time DMC spends resolving problems. All communication with the participating sites is handled by the DMC.

If missing or problematic data is detected, the DM sends an Additional Information Request (Z1 query letter) to the site RA or investigator specifying the problem and requesting clarification. The DM updates the participant's data submission calendar with the Z1 due date to notify the site RA or investigator of when a response is expected. The calendar will be updated upon receipt of the query response.

12.3.5 Missing and Delinquent Data Submission

In addition to providing the investigator a data collection calendar for each case, the DMC periodically prompts institutions for timely submission of data through the use of a Forms Due Report. This report lists data items (e.g. forms, reports, and images) that are delinquent. It is distributed at regular intervals via the electronic mail system to both the RA and the investigator at each site. In addition to prompting clinicians to submit overdue data, the Forms Due Report helps to reconcile the DMC's case file with that of the RA and/or investigator. Future Forms Due Reports may be sent on an as-needed basis in addition to past due reports. The site investigator or RA may use the Forms Due and Future Due Reports as a case management tool. At any time, sites may run their own Forms Due Reports using the Site Operations Tool on the ACRIN web site.

12.3.6 Data Quality Assurance

The Biostatistics Center (BC) at Brown University will maintain a study database at its site for monitoring data quality and for performing analyses. These data are drawn directly from the permanent database at the DMC. The transfer of data between the DMC and the BC have been validated through a series of checks consisting of roundtrip data verification in which data are sent back and forth to verify that the sent data are equivalent to the received data. These checks are repeated at random intervals during the course of a given study. Any discrepancies and other data quality issues will be referred to the DMC for resolution, since only the DMC can correct the data file. No changes to the data will be made at the BC.

Data will be monitored to assess compliance with the protocol and to look for unforeseen trends that may be indicative of procedural differences among clinical sites. If patterns are discovered in the data that appear to arise from causes specific to an institution, the DMC will contact the site to resolve the problem. The ACRIN Protocol Development and Regulatory Compliance (PDRC) Department will be involved in this process as needed. If the BDMC and PDRC cannot reconcile the problem with the site, it will be brought to the ACRIN Quality Assurance (QA) Committee for further discussion and resolution.

13.0 STATISTICAL CONSIDERATIONS

13.1 RTOG Primary Endpoint

- Local-regional, progression-free (LRPF) rate at 2 years

13.2 RTOG Secondary Endpoints

- Time to local-regional progression (TTLRP), the interval from registration to date of local or regional progression;
- Overall survival (OS), the interval from registration to the date of death or censored at the date of data collection;
- Progression-free survival (PFS), the interval from the date of registration to the date of tumor progression locally, regionally, distantly, or death, whichever occurs first, or censored at the last date of data collection;
- Lung cancer cause-specific survival, the interval from the date of registration to the date of death directly from lung cancer, or censored at the last date of data collection if still alive. A patient will be considered of dying from lung cancer if he or she had evidence of disease progression at any site, without a direct evidence of other causes;
- Radiation-induced lung toxicity (RILT);
- Grade 3+ esophagitis or cardiac adverse events related to chemoradiation between a conventional RT plan and a PET/CT-guided adaptive RT plan, as measured by CTCAE, v. 4.

13.3 ACRIN Primary Endpoint

13.3.1 Relative change in SUV peak from the baseline to the during-treatment FDG-PET/CT to LRPF with a 2-year follow up

13.4 ACRIN Secondary Endpoints

- Baseline FMISO uptake (tumor-to-blood pool ratio) association with LRPF (i.e. the assessment of using baseline FMISO-PET uptake as a prognostic marker);
- Relative change in SUV peak from the baseline to the during-treatment FDG PET/CT and/or the baseline FMISO uptake (tumor-to-blood pool ratio) prediction of the differential benefit of the adaptive therapy, i.e. the association of PET uptake parameters with LRPF depending on the assigned treatment; uptake parameters can be useful in guiding therapies, i.e. predictive markers;
- Additional PET imaging uptake parameters (change of peak SUVs for FDG from pre- to during-treatment, max SUV or change of max SUVs for FDG from pre- to during-treatment, change in metabolic tumor volume, FMISO total hypoxic volume, FMISO tumor-to-blood pool ratio) prediction of OS, LRPF, and lung cancer cause-specific (LCS) survival as well as to explore the optimal threshold for differentiating responders from non-responders. The FMISO total hypoxic volume is defined as the number of pixels in the gross tumor volume with a tumor-to-blood pool ratio of > 1.2, EORTC or University of Michigan/Kong's response criteria.

13.5 Endpoints for Translational Research

13.5.1 Primary Endpoints

- 2-year LRPF;
- Treatment toxicity: Grade 2+ RILT

13.5.2 Secondary Endpoints

- Tumor control outcome, PFS, and OS;
- Adverse events of lung, heart, and esophagus

13.6 Stratification (8/19/13)

Patients will be stratified by the Stage (IIIA vs. IIIB), the size of the primary tumor (>5 cm vs. ≤ 5 cm), and histology (squamous vs. non-squamous).

13.7 RTOG Sample Size with Power Justification

The sample size calculation will address whether the experimental arm (Arm 2) will improve the 2-year LRPF rate, compared to the standard arm (Arm 1). We assume that the LRPF rate at 2 years of 50% is expected if the patients are treated by conventional RT, based on data from RTOG 0117. We hypothesize that an adaptive RT plan based on a PET/CT (Arm 2) will improve the rate of LRPF at 2 years to 70%, corresponding to an absolute 20% increase compared to Arm 1. The study will be a randomized phase II screening trial as proposed by Rubinstein, et al. (2005). The randomization of experimental and standard

arms is set as 2:1. With 117 eligible patients (78 in the experimental arm and 39 patients in standard arm), there will be 85% power to detect a 20% absolute increase in 2-year LRPF rate at a significance level of 0.15, using a 1-sided Z test for 2 proportions with one planned interim analysis. Adjusting the number of cases by 15% for ineligible patients, **a maximum of 138 patients is required for this trial.**

The randomization of experimental and standard arms is set as 2:1. The 2:1 randomization will allow more patients to be treated on the experimental arm and with only a small increase in sample size (increasing the sample size by 20 from a 1:1 randomization). Additionally, as the control arm is based on RTOG 0617, there will be results of 250 patients treated with this regimen. Furthermore, from the Michigan experience, patients are often attracted by the novel design of the experimental arm of this study, such as the high dose to the more active tumor, a shortened treatment course, and individualized adaptive treatment. A 2:1 randomization may improve patient recruitment by providing a doubled opportunity of enrolling onto the experimental arm.

For trials in the same patient population, the average monthly accrual rate to RTOG 0324 (a phase II single-arm study that met its accrual objective) was 6.3 cases. RTOG 0617 (randomized phase III) is currently accruing at 9.8 cases/month. Based on these rates, it is expected that the monthly accrual for this trial will be approximately 6 cases, excluding the first 6 months: no accrual is expected during the first 2 months of trial activation as institutions obtain IRB approval. A total accrual of 12 patients is expected during the next 4 months; and thereafter, monthly accrual is expected to reach 6 patients per month. Therefore, the target accrual should be completed within 27 months of study activation. If the average monthly accrual rate (excluding the first 6 months) is less than 3 patients, the study will be re-evaluated with respect to feasibility.

13.8 ACRIN Sample Size Consideration (12/5/12)

This section has been intentionally left blank.

13.9 RTOG Analysis Plan

13.9.1 Statistical Methods

For the primary endpoint of local-regional, progression-free rate, Kaplan-Meier plots for local-regional, progression-free rate for each treatment arm will be calculated and the 2-year local-regional, progression-free rates from these plots will be compared and tested using Z test for two proportions. Only local or regional progression at 2 years (based on central review) will be counted as events (failures). Patients who die or have a distant recurrence without a local or regional progression within 2 years will be censored at the date of death or distant recurrence (based on site reporting). Patients who were lost to follow up or withdrew consent before 2 year evaluation also will be censored at the last follow-up date or date of consent withdrawal.

TTLRP for 2 treatment arms also will be estimated through a cumulative incidence approach with death and distant recurrences treated as competing events; events for this endpoint are local or regional progression. For hypothesis testing with the difference in TTLRP between 2 treatment arms, a log rank test will be used in which death and distant recurrences prior to local-regional progression are treated as censored observations.

OS and PFS rates will be estimated using the Kaplan-Meier method, and differences between treatment arms will be tested in the log rank test. OS will be measured from the date of registration to the date of death or otherwise, the last follow-up date on which the patient was reported alive. PFS will be measured from the date of registration to the date of first progression (local, regional, or distant) or death or otherwise, the last follow-up date on which the patient is reported alive. Differences in observed severities of toxicities (grade 3+) between groups will be tested using a chi square test.

Multivariate analyses with the Cox proportional hazard model for OS and PFS will be performed with the stratification variables as fixed variables to assess the treatment effect adjusting patient-specific risk

factors. The covariates evaluated for the multivariate models are: assigned protocol treatment and other prognostic factors. Proportional hazard assumptions will be checked using different graphical or time-varying coefficients testing methods. If the data clearly do not follow proportional hazards, other statistical models will be used to fit the data instead. Possible alternatives are to use the stratified Cox proportional hazard model, accelerated failure model, or partition the time axis into sections where proportional hazard assumption holds.

An event for the study endpoint of lung cancer cause-specific survival is death due to lung cancer. Since this endpoint is a cause-specific failure where death due to other reasons is a competing risk, the cumulative incidence method will be used to estimate cumulative incidence of death due to lung cancer. Gray's test will be used to compare the cumulative incidences in the 2 treatment arms. Fine and Gray's proportional subdistribution hazard regression model will be used to assess the effects of covariates on the lung cancer cause-specific survival.

13.9.2 Interim Analysis to Monitor Study Progress

Interim reports with statistical analyses are prepared every 6 months until the initial manuscript reporting the treatment results has been submitted. The reports contain:

- Patient accrual rate with a projected completion date (while the study is still accruing)
- Total patients accrued
- Distributions of important pretreatment and prognostic baseline variables
- The frequencies and severity of adverse events by treatment arm
- Compliance rates of treatment delivery

The interim reports will not contain the results from the treatment comparisons with respect to the efficacy endpoints (2-year LRPF rate, TTLRP, OS, PFS, etc.). The RTOG Data Monitoring Committee (DMC) will review the accrual to the study and the rate of adverse events on the study at least twice per year until the initial results of the study have been presented to the scientific community.

The first eligible and evaluable 20 patients receiving any treatment in the experimental arm (Arm 2) will be closely monitored to assure that patients on that arm are receiving the correct treatment. If six or more of the first 20 patients experience clinically severe RILT (grade 3+), which occurs within 30 days after the end of all protocol treatment, the trial will be halted due to lack of safety. The operating characteristics of the trial are determined from the binomial distribution as follows: the therapeutic plans have a target rate of lung toxicity of no more than 0.172. If that is the true probability of lung toxicity, the stopping rule will halt the trial with a probability of 0.11. If the probability of lung toxicity is actually 0.33, the trial will be halted with a probability of 0.69. If the probability of lung toxicity is 0.37 or greater, the probability the trial will be halted is at least 0.81.

To doubly ensure the safety of this trial, the rates of grade 3+ RILT between the arms will be compared after 50% of the eligible and evaluable patients who receive any protocol treatment (19 in standard arm and 38 in experimental arm) have been accrued to the trial. With 57 patients randomized into the 2 arms, we will have 80% power to detect the following difference in the rates of grade 3+ RILT occurring within 30 days after the end of all protocol treatment at the significance level of 0.05 (one-sided): 5% vs. 33%, 10% vs. 40%, and 15% vs. 47%. If the p-value related with this comparison is less than 0.05 (one-sided), the trial will be halted due to safety concerns.

In addition to RILT, the survival rates in both treatment groups will be examined to assess safety once half of the patients (39) have been accrued to Arm 2 (experimental arm) and have experienced 3 months of follow up. Overall survival, along with confidence intervals, will be estimated. Applying data from RTOG 0617, if the upper bound of the confidence interval is not above 95%, then the study statistician will look at the data to determine if the study will be halted due to safety concerns. The survival rate and corresponding confidence intervals also will be estimated for Arm 1 (standard arm) to be used as a reference, but the estimates will not be compared due to the lower sample size in Arm 1 from the 2:1 randomization.

13.9.3 Significance Testing for Early Termination and/or Reporting

A group sequential test with one planned interim analysis and a final analysis will be performed. The interim analysis will be based on the primary endpoint as defined in Section 13.1.1, and thus will be carried out once 57 patients have had 2 years of follow up. At the planned interim analysis, the z-value from the two-sample test for two proportions assessing treatment futility with respect to the primary endpoint, LRPF rate, will be compared to the z-value generated from the futility testing boundary. The

O'Brien & Fleming boundary from the Lan-DeMets family, will be applied due to its more conservative nature, If the p-value associated with the resulting test statistic is less than or equal to the p-value associated with the futility boundary for rejecting H_1, then we will stop accrual to the trial (if applicable) and will report that we cannot conclude that the LRPF rate of the experimental arm (Arm 2) is higher than that of the control arm (Arm 1). If this boundary is not crossed, accrual (if applicable) and follow-up will continue until the final analysis. The p-values and associated Z-score futility boundary for early stopping are as depicted in the table below.

Interim Analysis for LRPF Rate

Information Time	Cumulative Number of Patients in Both Arms	Futility: Reject H_1 if p >	Futility Boundary: Reject H_1 if critical value <
0.5	59	0.597	-0.246
1.0	117	0.159	1.010

At the protocol-planned interim analysis, the results from the test assessing the treatment futility will be reported to the RTOG DMC. The responsible statistician may recommend early reporting of the results and/or stopping accrual (if applicable) of the trial if the critical value is less than the futility boundary provided in the table above. The accrual rate, treatment compliance, safety of the treatments, and the importance of the study also are considered in making such a recommendation. The results will be reported to the RTOG DMC with the treatment blinded. The DMC will then make a recommendation about the trial to the RTOG Group Chair.

13.9.4 Significance Testing for Final Analysis

The final analysis will be performed on an intent-to-treat basis, such that all eligible cases will be included in the arm to which the patient was randomized regardless of what treatment the patient actually received. The analysis to report the final results of treatment will be undertaken when each randomized patient has been potentially followed for a minimum of 2 years. A 1-sided Z test for 2 proportions at the 0.15 significance level will be performed to test the difference in 2-year LRPF rate between the 2 treatment arms. If the p-value is less than the protocol-specified 0.15 (1-sided), the study statistician will reject the null hypothesis and conclude that the experimental arm (Arm 2) has a better 2-year LRPF rate than the standard arm (Arm 1), therefore supporting the development of a phase III trial comparing this regimen to the current standard at that time. All information reported in the interim analyses to monitor the study progress (Section 6.4.2) and the treatment compliance also will be included in the final report.

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.10 ACRIN Statistical Design for Imaging as a Biomarker

This section has been intentionally left blank.

13.11 Statistical Considerations for Translational Research

To study 2-year tumor control and treatment toxicity for aim #1 and #2 of this correlative research study, we will use logistic models to examine the relationship between local-regional failure, toxicity events, baseline levels of ACE, IL6, and TGFß1, IL-8, and other cytokine or proteomic markers. In addition, the Generalized Estimating Equation (GEE) method will be used to explore the relationship between tumor control, treatment toxicities, and marker levels measured during treatment. Comparison of model accuracy will be determined by area under curve (AUC) of the receiver-operative curves of various predictive models.

For exploratory analysis of tumor progression-free survival and overall survival analysis, we will examine whether patients with normal baseline levels of biomarkers have a different prognosis than patients with

abnormal baseline levels by calculating the product-limit estimates of the survival function and comparing those estimates using the log-rank statistic. For subsequent blood draws, a landmark analysis will be performed comparing the product-limit estimates among the subset of patients still at risk at a specific time point. The relationship between progression-free survival, overall survival, and abnormal baseline marker levels also will be explored by fitting Cox proportional hazards regression models, both adjusted for baseline disease and patient characteristics and unadjusted. For biomarker values obtained from blood draws during RT and 4-6 weeks after treatment, Cox models will be fit treating the marker value as a time-dependent covariate. Assuming usable baseline blood samples can be obtained from 134 patients, this will provide at least modest power (> 95%) to detect large differences (hazard ratios > 1.5) between patients with normal and abnormal marker levels.

13.12 Gender and Minorities

Some investigators have shown gender to be a prognostic factor in non-small cell lung cancer; however, the RTOG did not show this to be the case. An analysis of race also did not indicate an association with outcome (Graham 1992; Scott 1997). In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have also considered the possible interactions between gender and treatments and race and treatments. Participation rates of men and women will be examined in the interim analyses. Based on accrual statistics from RTOG 0617, the following table lists projected accrual by gender and race/ethnicity.

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	2	3	5
Not Hispanic or Latino	55	78	133
Ethnic Category: Total of all subjects	57	81	**138**
Racial Category			
American Indian or Alaskan Native	1	0	1
Asian	2	1	3
Black or African American	6	8	14
Native Hawaiian or other Pacific Islander	0	0	0
White	48	72	120
Racial Category: Total of all subjects	57	81	**138**

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APPENDIX I: STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS (2/25/14)

*See Section 11.1 for details

Assessments	**Pre-treatment: Prior to Registration** (unless noted otherwise)		
	Within 6 wks	**Within 4 wks**	**Within 2 wks**
History/physical			X
Thoracic Surg eval	Within 8 wks		
Documentation of weight			X
Performance status			X
*FDG-PET/CT scan	Baseline: Within 28 days prior to treatment		
*FMISO-PET/CT scan	Baseline: Within 28 days prior to treatment		
*CT scan or sim CT of chest, upper ab (IV contrast is recommended unless medically contraindicated)	X		
*CT of brain (contrast is recommended unless medically contraindicated) or MRI of brain	X		
CBC w/ diff & ANC			X
Creatinine			X
Serum pregnancy test (if applicable)			Within 3 days
*PFTs	X		
Electrolytes, complete panel			Within 2 wks prior to treatment
Pulmonary consult	6 weeks prior to treatment: Highly recommended, but optional		
EKG and/or Echo			
Lung ventilation/perfusion scan +/- CT scan			
Nutrition Assessment			
†Tissue for banking	X		
†Blood for research	Prior to treatment		

†For patients who consent to participate in the specimen components of the study.

APPENDIX I: STUDY PARAMETER TABLE: ASSESSMENTS DURING TREATMENT (8/19/13)
*See Section 11.1 for details

Assessments	During Treatment	
	Weekly during RT/Chemo	During Continued Concurrent Chemo
History/physical	X	On day 1 of each cycle
Documentation of weight	X	On day 1 of each cycle
Performance status	X	
*FDG-PET/CT scan	*X	
CBC w/ diff & ANC	X	Weekly
Electrolytes (complete panel), creatinine	X	On day 1 of each cycle
Liver function tests	X	
Adverse event eval	See Sec. 11.1.2	X
†Blood for research	Weeks 2 and 4	

†For patients who consent to participate in the specimen components of the study.

APPENDIX I: STUDY PARAMETER TABLE: ASSESSMENTS IN FOLLOW UP (2/25/14)
*See Section 11.1 for details

Assessments	Follow Up			
	1 & 3 mos. after end of protocol treatment	6, 9, 12 mos. after end of protocol treatment	18, 24, 30, 36 mos. after end of protocol treatment	48 & 60 mos. after end of protocol treatment & annually
History/physical	X	X	X	X
Documentation of weight	X	X	X	X
Performance status	X	X	X	X
*FDG-PET/CT scan	*X	-	-	
*CT scan of chest, upper ab with IV contrast		q3 mos. in 1st year; q6 mos. in 2nd year; see Section 11.1.3 for patients who exhibit tumor progression.		
CT with contrast of brain or MRI of brain		As clinically indicated		
Chest x-ray	X	*X		
CBC w/ diff & ANC	X	X	X	X
Electrolytes (complete panel), creatinine	X	X	X	X
Liver function tests	X	X	X	X
*PFTs	At 3-4 mos.	At 12 mos.		
Bronchoscopy	*X			
Tumor response eval	*X	*X	*X	*X
Adverse event eval	X	X	X	X
†Blood for research	At 3 mos. after end of protocol treatment			

†For patients who consent to participate in the specimen components of the study.

APPENDIX II: ZUBROD PERFORMANCE SCALE

0	**Fully active, able to carry on all predisease activities without restriction**
1	**Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work**
2	**Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours**
3	**Capable of only limited self-care, confined to bed or chair 50% or more of waking hours**
4	**Completely disabled. Cannot carry on self-care. Totally confined to bed**
5	**Death**

APPENDIX III: AJCC STAGING SYSTEM

Edge, SB, ed. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

LUNG

Primary Tumor (T)

TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy

T0 No evidence of primary tumor.

Tis Carcinoma *in situ*

T1 Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*

T1a Tumor 2 cm or less in greatest dimension

T1b Tumor more than 2 cm but 3 cm or less in greatest dimension

T2 Tumor more than 3 cm but 7 cm or less with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less): Involves main bronchus, 2 cm or more distal to the carina; Invades the visceral pleura PL1 or PL2); Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T2a Tumor more than 3 cm but 5 cm or less in greatest dimension

T2b Tumor more than 5 but 7 cm or less in greatest dimension

T3 Tumor more than 7 cm or one that directly invades any of the following: parietal (PL3), chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (less than 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe

T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodules in a different ipsilateral lobe

*The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph nodes metastasis

N1 Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension

N2 Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)

N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant Metastasis (M)

M0 No distant metastasis

M1 Distant metastasis

M1a Separate tumor nodule(s) in a contralateral lobe tumor with pleural nodules or malignant pleural (or pericardial) effusion*

M1b Distant metastasis

* Most pleural (and pericardial effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element, and the patient should be classified as M0.

STAGE GROUPING	
Occult Carcinoma	TX, N0, M0
Stage 0	Tis, N0, M0
Stage IA	T1a-b, N0, M0
Stage IB	T2a, N0, M0
Stage IIA	T2b, N0, M0
	T1a-b, N1, M0
	T2a, N1, M0
Stage IIB	T2b, N1, M0
	T3, N0, M0
Stage IIIA	T1a-b, N2, M0
	T2a-b, N2, M0
	T3, N1-2, M0
	T4, N0-1, M0
Stage IIIB	T1a-b, N3, M0
	T2a-b, N3, M0
	T3, N3, M0
	T4, N2-3, M0
Stage IV	Any T, Any N, M1a-b

APPENDIX IV: BIOSPECIMEN COLLECTION (12/19/13)

Shipping Instructions:

U.S. Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
(2340 Sutter Street, Room S341)
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For All Frozen, Overnight, or Trackable Specimens
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

- ❑ Include all RTOG paperwork in pocket of biohazard bag.
- ❑ Check that the Specimen Transmittal (ST) Form has the consent boxes checked off.
- ❑ Check that all samples are labeled with the RTOG study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

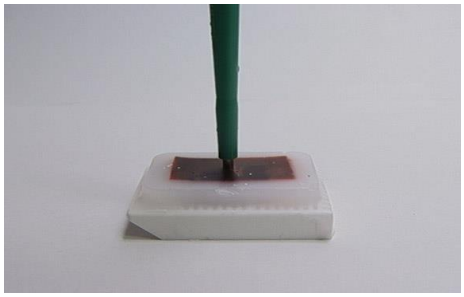
- ❑ **FFPE Specimens:**
  - ○ Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
  - ○ FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap or gauze. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear the block shaking it is likely that they might break during shipping.
  - ○ Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice**.

- ❑ **Frozen Specimens**:
  - ○ Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified. If possible, keep serum, plasma, and whole blood in separate bags.
  - ○ Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs.). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - ○ Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - ○ Send frozen specimens on dry ice via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80C until ready to ship.

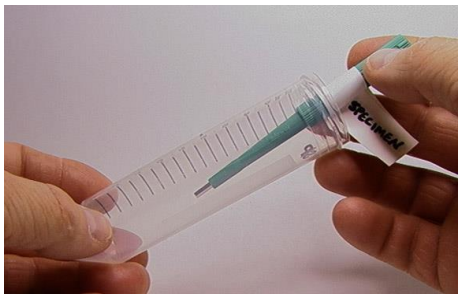
- ❑ **For Questions regarding collection/shipping please contact the RTOG Biospecimen Resource by e-mail: RTOG@ucsf.edu or phone: 415-476-7864 or Fax: 415-476-5271.**

APPENDIX IV (Continued)
RTOG FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for submission to the RTOG Biospecimen Resource. The plug kit contains a shipping tube and a punch tool.

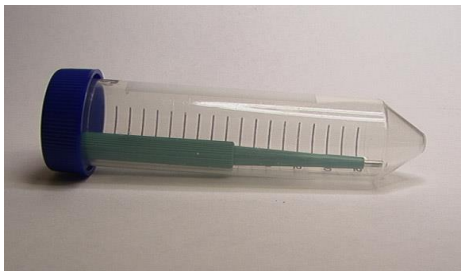


Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.



Step 2
Label the punch tool with the proper specimen ID. DON'T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or e-mail us if you have any questions or need additional specimen plug kits.



Step 3
Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

***NOTE:** If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the RTOG Biospecimen Resource and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.

Ship specimen plug kit, specimen in punch tool, and all paperwork to the address below. For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the RTOG Biospecimen Resource by e-mail: RTOG@ucsf.edu or call 415-476-7864/Fax 415-476-5271.

U.S. Postal Service Mailing Address: Only for non-urgent, ambient specimens: FFPEs, slides, blocks
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
(2340 Sutter Street, Room S341)
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For All Frozen, Overnight, or Trackable Shipments
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

This Kit is for collection, processing, storage, and shipping of serum, plasma, or whole blood.

Kit contents: NOTE: The RTOG Biospecimen Resource provides the blood draw tubes for the 1st collection time point, as the tubes do expire. If a site requires additional blood draw tubes for the remaining time points, please contact the Biospecimen Resource after the patient is enrolled, and additional tubes will be sent.

- One Red Top tube for serum (A)
- One Purple Top EDTA tube for plasma (B)
- One Purple Top EDTA tube for Whole Blood (C)
- Twenty-five (25) 1 ml cryovials
- Biohazard bags (3) and Absorbent shipping material (3)
- Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form (ST) and Kit Instructions

PREPARATION AND PROCESSING OF SERUM, PLASMA AND WHOLE BLOOD:

(A) Serum: Red Top Tube

- ❑ Label as many 1ml cryovials (5 to 10) as necessary for the serum collected. Label them with the RTOG study and case number, collection date, time, and time point, and clearly mark cryovials "serum".

Process:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST.
3. Aliquot **0.5 mL serum** into as many cryovials as are necessary for the serum collected (5 to 10) labeled with RTOG study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as "serum".
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90° C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90° C until ready to ship on dry ice. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the ST.

(B) Plasma: Purple Top EDTA tube #1

- ❑ Label as many 1ml cryovials (5 to 10) as necessary for the plasma collected. Label them with the RTOG study and case number, collection date, time, and time point, and clearly mark cryovials "plasma". **Note: It is critical to follow the exact plasma processing instructions for this protocol. Any deviations from the protocol must be noted on the ST.**

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Place samples on ice or at 4°C immediately.
3. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at 2500-3000g for 30 minutes at 4°C (**critical**). If sites are unable to process samples at 4°C then spinning at room temperature is only acceptable if done within 30 minutes of draw and must be noted on the ST.
4. Carefully pipette and aliquot **0.5 mL plasma** into as many cryovials as are necessary for the plasma collected (5 to 10) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as "plasma". Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C.
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the ST.

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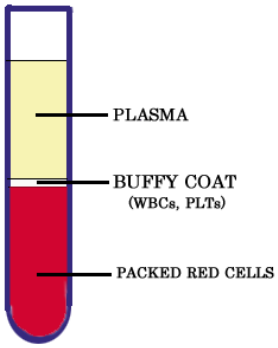

(C) <u>Whole Blood for DNA: Purple Top EDTA tube #2</u>

- ❑ Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected. Label them with the RTOG study and case number, collection date/time, and time point, and clearly mark cryovials "blood".

<u>Process</u>:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot **1.0 mL blood** into as many cryovials as are necessary for the blood collected (3 to 5) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on ST.

<u>Freezing and Storage</u>:

- ☐ Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- ❑ Store at –80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  <u>OR</u>:
  - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).

  <u>OR</u>:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- ❑ Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

<u>Shipping/Mailing</u>:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all RTOG paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- ❑ Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.

(continued on next page)

- *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- **For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail RTOG@ucsf.edu or call 415-476-7864.**

Shipping Address:

Courier Address (FedEx, UPS, etc.): For All Frozen, Overnight, or Trackable Shipments
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476-7864 or e-mail: RTOG@ucsf.edu

APPENDIX V: FMISO-PET/CT IMAGE SUBMISSION (2/25/14)

Imaging examinations must be submitted to the ACRIN-Image Management Center (IMC) immediately after each time point.

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

A completed, signed Image Transmittal Worksheet (ITW) MUST accompany all imaging exams submitted to ACRIN for each time-point. The Image Transmittal worksheet can be found on the ACRIN web site for this study under Protocol Summary Table at http://www.acrin.org/6697_protocol.aspx.

For exams submitted via electronic transmission, complete this worksheet and fax to (215) 923-1737. For exams submitted via media, complete this worksheet and include with the media shipment. Please affix a label to the jacket of the media to include: study name, site name, NCI inst., code, case no., date of exam, time point, and type of imaging. Do not affix labels directly to the disk.

Images on CD or DVD-ROM, should be shipped to:

ACRIN Image Archive
American College of Radiology
1818 Market Street, Suite 1600
Philadelphia, PA 19103
Attn: ACRIN 6697

ACRIN can provide software (TRIAD) for installation on a PC at your site that collects, anonymizes and submits image sets from your PET/CT system or from your PACS. The images are “Digital pushed” either from the PET/CT system or from the PACS to the PC on which the software is installed. This software anonymizes and encrypts images as they are transferred via FTP to the ACRIN image archive. For more information, see https://triad.acr.org.

TRIAD Image Submission software PC requirements:

1. Network capability to transmit data from a scanner to a linked workstation, PC, or PACS
2. A Windows XP PC available to transmit data (patient data, MR and PET image data) to ACRIN:
a. Operating System Windows XP Pro
b. Access to the Internet: Internet Explorer
c. Minimum of 50 GB available hard drive
d. At least 1 GB RAM
e. Ability to view PDF documents
3. Software utilities required:
a. Windows Installer 3.1
b. Microsoft .NET framework 2.0
c. MDAC Type 2.8
d. MS SQL 2005 Express

Please contact the TRIAD help desk (Triad-Support@ acr.org**) or 215-940-8820 regarding installation requirements and to arrange the installation of TRIAD software prior to first accrual.**

For questions regarding site qualification, image acquisition or image submission, contact Adam Opanowski CNMT, RT (N), lead technologist for this trial at: imagearchive@ acr.org **or 215-574-3238.**

APPENDIX VI: FMISO-PET/CT ADVERSE EVENT REPORTING INSTRUCTIONS

1.0 Definition of Adverse Event

An Adverse Event **(AE)** is any untoward, undesired, unplanned medical occurrence in a participant, and does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or physiological observation), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). Any symptom, sign, illness, or experience that develops or worsens in severity during the course of the study, including intercurrent illnesses or injuries, should be regarded as an AE.

2.0 Definition of Serious Adverse Event

AEs are classified as serious or non-serious. A Serious Adverse Event **(SAE)** is any AE that results in any of the following outcomes:

- Death;
- Life-threatening (refers to any adverse event that places the subject at immediate risk of death from the event as it occurred; life-threatening event does not include an event that, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death);
- Inpatient hospitalization and/or prolongation of an existing hospitalization (hospitalization is defined as lasting 24 hours or longer. Emergency room visits are not considered serious until one of the above criteria is met. Any elective hospitalization for a pre-existing condition that has not worsened does not constitute an SAE;
- Results in persistent or significant disability or incapacity (substantial disruption in a person's ability to conduct normal daily living activities);
- A congenital anomaly or birth defect (in offspring); or
- Other medically important event.

Important medical events are those based upon appropriate medical judgment that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above.

3.0 Adverse Event Grading

Grade refers to the severity (intensity) of the AE.

1 – Mild: AE is noticeable to the participant but does not interfere with routine activity.
2 – Moderate: AE interferes with routine activity but responds to symptomatic therapy and/or rest
3 – Severe: AE significantly limits the subject's ability to perform routine activities despite symptomatic therapy
4 – Life-threatening or disabling
5 – Death/Fatal

4.0 Adverse Event Attribution

Attribution is the determination of whether an AE is related to the FMISO-PET/CT imaging study.
Attribution categories are:

Definite	–	AE **is clearly related** to the study treatment or procedure.
Probable	–	AE **is likely related** to the study treatment or procedure.
Possible	–	AE **may be related** to the study treatment or procedure.
Unlikely	–	AE **is doubtfully related** to the study treatment or procedure.
Unrelated	–	AE **is clearly NOT related** to the study treatment or procedure.

5.0 Expected Adverse Events for FMISO-PET/CT Imaging Study:

5.1 Expected Adverse Events Associated With Standard of Care Practice

Any AE that is a result of standard-of-care practice will be reported and managed per the institution's policies and procedures.

5.2 Expected Adverse Events Associated With the Intravenous (IV) Catheter Placement for Injection of FMISO:

- Hemorrhage (hematoma at the injection site);
- Infection (catheter related infection) at the injection site;
- Minor discomfort;
- Bleeding;

- Infection;
- Bruising.

5.3 Expected Adverse Events and Potential Risks Associated with FMISO:

- None

5.4 Expected Adverse Events from PET Scan:

- Discomfort;
- Claustrophobia.

5.5 Expected Adverse Events from CT Scan:

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

NOTE: As of July 14, 2008, FDA released a preliminary public health notification of possible malfunction of electronic medical devices caused by CT scanning. Site should use CT scout views to determine if implanted or externally worn electronic medical devices are present and if so, their location relative to the programmed scan range. Refer to the FDA web site for the notification (www.fda.gov/cdrh/safety/071408-ctscanning.html) and their recommendations.

6.0 Recording of Adverse Events

At each contact (site visit and/or telephone) with the study participant, the investigator or investigator-designee must seek information on AEs through discussion and, as appropriate, by examination. Information on all expected and unexpected AEs considered possibly, probably, definitely related to the FMISO-PET/CT imaging sub-study with the severity level of grades 3, 4, 5 should be recorded immediately into the source document, e.g. AE Log and/or progress notes of the study participant's chart, and retained at the site. These AEs will also be recorded in the AE CRF and reviewed by the principle site investigator in real time to determine grade and attribution of the event. For the standard MR imaging, sites should follow standard of care practice per the local institution's policies and procedures.

7.0 Reporting of Adverse Events

Prompt reporting of all AEs is the responsibility of each investigator, clinical research associate, and nurse engaged in clinical research. Routine reporting is defined as documentation of AEs on source documents and AE CRF, and submission to RTOG for preparation of a report for Data and Safety Monitoring Committee (DSMC) review, quarterly reports to CDUS, and the final study report. Expedited reporting is defined as immediate notification of NCI and RTOG. If reporting an event related to the FMISO-PET/CT Imaging component, immediate notification to ACRIN is also required. Routine reporting requirements also apply. ACRIN will collect and report only those AEs considered possibly, probably, or definitely related to the FMISO- PET/CT Imaging sub-study that occur during study participation and up to 30 days after the last study procedure. Local IRBs and/or institutions may stipulate additional adverse events reporting based upon their review of the protocol. All expected and unexpected adverse events considered possibly, probably, or definitely related to FMISO- PET/CT Imaging sub-study and SAEs will be documented in the study participant's chart and AE CRFs, in addition to meeting all study-specific reporting requirements of ACRIN, NCI/CIP, and the local IRB (per local IRB policy).

8.0 Expedited Reporting to NCI, RTOG, and/or ACRIN

8.1 Investigator or investigator-designee must use expedited AE reporting for **deaths** (considered possibly, probably, or definitely related to the FMISO-PET/CT Imaging sub-study) occurring during study participation and up to 30 days after the last study procedure.

8.2 All life-threatening/disabling unexpected AEs (considered possibly, probably, or definitely related to the FMISO-PET/CT Imaging sub-study) occurring during study participation and up to 30 days after the last study procedure will reported within 24 hours, followed by a full report within five (5) calendar days of first knowledge of the event.

8.3 All hospitalizations (or prolongation of existing hospitalization) for AEs with the severity (intensity) level of CTCAE (4.0) grade 3, 4, 5 and attribution of possibly, probably, or definitely related to the FMISO-PET/CT Imaging sub-study must be reported within ten (10) calendar days of first knowledge of the event, in addition to documentation in patient chart and AE CRF. However, if the event is grade 4 or 5 and unexpected, it must be reported within 24 hours, followed by a full report within five (5) calendar days.

8.4 All other SAEs with attribution of possibly, probably, or definitely related to the FMISO-PET/CT Imaging sub-study which include AEs that results in persistent or significant disability or incapacity, or congenital anomaly (birth defect) in the offspring of the study participant must be reported within ten (10) calendar days of first knowledge of the event during study participation and up to 30 days after the last study procedure, in addition to documentation in patient chart and AE CRF.

8.5 Significant new information and/or follow-up information (e.g., test results, autopsy, and discharge summary) on on-going SAEs should be promptly reported.

8.6 When to Report an Event in an Expedited Manner (2/25/14)

Some AEs require 24-hour notification. Please complete a 24-Hour Notification Report via the NCI CTEP-AERS web site (https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613) within 24 hours of learning of the event. The full CTEP-AERS report must be completed and submitted via CTEP-AERS within 5 calendar days.

If the CTEP-AERS system is down, a 24-hour notification call must be made to TRI 301-897-1704 and ACRIN 215-717-2763 for any AE related to the FMISO-PET/CT Imaging sub-study. Once the system is restored, a 24-hour Notification Report must be entered into the CTEP-AERS system by the original submitter of the report at the site.

When an AE requires expedited reporting, submit a full CTEP-AERS report within the timeframes outlined in the table below. **NOTE:** AEs that meet the reporting requirements and occur within 30 days of the last dose of protocol treatment or procedure (FMISO-PET/CT Imaging sub-study) must be reported on an expedited AE report form (using CTEP-AERS).

For any AEs that occur more than 30 days after the last dose of treatment or procedure (FMISO-PET/CT Imaging sub-study), only those that have an attribution of possibly, probably, or definitely AND meet the reporting requirements as described in the table below must be reported on an expedited AE report form (using CTEP-AERS).

The following table summarizes the reporting requirements for AEs for the FMISO-PET/CT Imaging sub-study:

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

7) Death
8) A life-threatening adverse event
9) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
10) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
11) A congenital anomaly/birth defect.
12) 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days

Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

9.0 Other Recipients of AE Reports (2/25/14)

CTEP-AERS reports will be forwarded to the appropriate regulatory agencies and/or pharmaceutical company, if applicable.

Prompt reporting of AEs is the responsibility of each investigator, clinical RA, and/or nurse engaged in clinical research. Anyone uncertain about whether a particular AE should be reported should contact the ACRIN headquarters at 215-574-3150 for assistance.

Adverse events (AEs) meeting the criteria in the tables below, including all serious adverse events (SAEs) will be reported to the Cancer Imaging Program (CIP) as directed in this section.

CTEP-AERS is an electronic, internet based Adverse Event reporting system operated by NCI/CTEP. It is generally used to capture and disseminate information on relatively significant Adverse Events, based upon trial stage, expectedness, severity, and attribution. However, it may be used to report adverse events of all types if CTEP-AERS reporting is required per protocol.

The electronic-CTEP-AERS system is to be used for all 'expedited reporting' events as defined herein. If the system is temporarily unavailable, a paper and telephone/FAX based process is provided herein. Expedited AE data is to be re-submitted via the electronic CTEP-AERS system as soon as is possible in cases where temporary e-CTEP-AERS unavailability has necessitated manual capture and submission.