

AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK
ACRIN 6668/RTOG 0235

Positron Emission Tomography Pre- and Post-treatment Assessment for Locally Advanced
Non-small Cell Lung Carcinoma

Study Chair

Mitchell Machtay, M.D.
Case Western Reserve University
Department of Radiation Oncology
11100 Euclid Ave. – Lerner Tower B181
Cleveland, OH 44106
Phone #216-844-2530
Mitchell.Machtay@uhhospitals.org

Image Guided Therapy Co-chair

Jeffrey Bradley, M.D.
Dept. of Radiation Oncology
Washington University
4939 Children's Place, Suite 500
St. Louis, MO 63110
Phone # 314-362-8525
Fax # 314-362-8521
bradley@radonc.wustl.edu

Nuclear Medicine Co-chairs

Barry A. Siegel, M.D.
Division of Nuclear Medicine
Mallinckrodt Institute of Radiology
510 S. Kingshighway Blvd.
St. Louis, MO 63110
Phone # 314-362-2809
Fax # 314-362-2806
siegelb@mir.wustl.edu

Abass Alavi, M.D.
Univ. Pennsylvania Nuclear Medicine Dept.
3 Donner Bldg., 3400 Spruce St.
Philadelphia, PA 19104
Phone # 215-662-3069
Fax # 215-349-5843
alavi@rad.upenn.edu

Nuclear Medicine Physics Co-chair

Janet S. Reddin, Ph.D.
Univ. Penn. Nuclear Medicine Dept.
110 Donner Bldg, 3400 Spruce St.
Philadelphia, PA 19104
Phone # 215-662-3095
reddin@upenn.edu

Thoracic Radiology Co-chair

Reginald Munden, M.D.
Department of Radiology
University of Alabama at Birmingham
619 19th Street South
Birmingham, AL 35249
Phone # 205-934-9577
Fax # 205-934-8110
rmunden@uabmc.edu

Statistician

Zheng Zhang, Ph.D.
Center for Statistical Sciences
Brown University
121 South Main Street, Box G-S121-7
Providence, RI 02912
Phone # 401-863-2578
Fax # 401-863-9182
zzhang@stat.brown.edu

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

Original Protocol Date: September 27, 2004
Activation Date: March 1, 2005
Current Version Date: March 2, 2010
Includes Amendment 1 - 7

This protocol was designed and developed by the American College of Radiology Imaging Network (ACRIN). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by ACRIN nor does ACRIN assume any responsibility for unauthorized use of this protocol.

INDEX

Schema

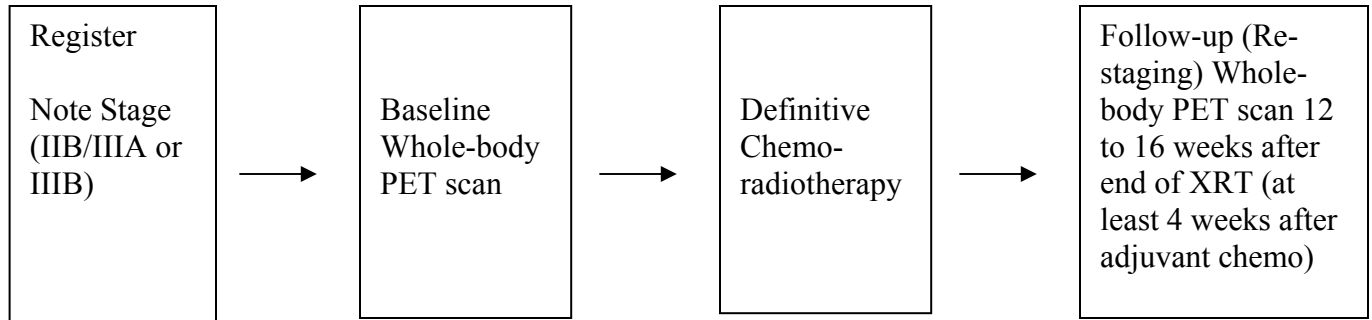
1.0	Abstract.....	4
2.0	Background and Significance.....	4
3.0	Specific Aims.....	7
4.0	Study Overview.....	8
5.0	Participant Selection.....	8
6.0	Site Selection.....	10
7.0	Online Registration System.....	12
8.0	Data Collection and Management.....	13
9.0	Data Collection Forms.....	16
10.0	Image Submission.....	16
11.0	Diagnostic Evaluation of Study Participants.....	17
12.0	Radiation Therapy.....	23
13.0	Drug Therapy.....	26
14.0	Pathology/Translational Research.....	27
15.0	Statistical Considerations REMOVED FROM WEB VERSION	28
16.0	Adverse Event Reporting.....	32
17.0	Institutional Audits.....	37
	References	41
Appendix I:	Sample Informed Consent Form.....	45
Appendix II:	Eligibility Check and Registration Questions.....	51
Appendix III:	Credentialing Procedures of PET Imaging for This Study.....	56
Appendix IV:	PET Imaging Quality Control Standards.....	57
Appendix V:	Institution Participation Guidelines.....	58
Appendix VI:	CT Acquisition Parameters.....	59
Appendix VII:	ACRIN 6668 Protocol-Specific Application Information.....	60

AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 6668/RTOG 0235

Positron Emission Tomography Pre- and Post-treatment Assessment for Locally Advanced Non-small Cell Lung Carcinoma

SCHEMA



Participants will be followed up for outcomes for 3 years beyond the end of the accrual period.

Eligibility (see Section 5.0 for details)

- Stage IIB or III non-small cell lung carcinoma being treated with definitive chemoradiation (inoperable).
- Participant may be treated on another protocol or treated with conventional concurrent NSCLC chemoradiation.
- Zubrod performance status 0-1.
- No prior thoracic radiotherapy.
- Age ≥ 18 .
- Able to tolerate PET imaging.
- Study specific informed consent.
- Women should not be pregnant and all participants must use medically appropriate birth control.

Required Sample Size: 250 participants, including at least 75 with stage IIB/IIIA and at least 75 with stage IIIB disease.

1.0 ABSTRACT

Background/Rationale (See Section 2 for detailed background and references): The current standard of care for patients with unresectable clinical stage III (and medically inoperable stage II) non-small cell lung carcinoma (NSCLC) is combined chemoradiation therapy, which offers a median survival of approximately 17 months and 3-year survival of about 25%. This is a significant improvement over historical baseline treatment with radiotherapy or surgery alone, but still quite poor. New strategies are being intensely studied for this disease. One limitation of the new therapies is the difficulty in assessing their efficacy in a timely fashion. Computed tomography (CT) is the standard method of assessing response to chemoradiation but can be very difficult to interpret in the setting of evolving radiation effects on the lung and other tissues. Positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET) has been shown to be complementary and/or superior to CT for initial staging of NSCLC. One potential advantage of FDG-PET is the ability to analyze abnormal results quantitatively based on the standardized uptake value (SUV), which may be a marker of disease activity. Small, single-institutional studies have suggested that post-treatment FDG-PET-SUV is useful at predicting long-term outcome, but a multi-institutional study is necessary to confirm these data. If confirmed in this study, the SUV measured on FDG-PET may become a routinely used, quantifiable, and analytical early indicator of disease activity and efficacy of treatment. This would allow for clinicians and clinical researchers to make rational decisions (such as starting a new chemotherapy program in an individual patient, or determining that a regimen is not worthy of further study in the research setting) before long-term survival data matures.

The primary purpose of this study is to determine if the SUV determined by FDG-PET shortly after treatment is a useful predictor of long-term clinical outcome (survival) after definitive chemoradiotherapy. Secondary endpoints are outlined in Section 3.2.

Eligible patients are those with AJCC clinical stage IIB/III non-small cell lung carcinoma who are being planned for definitive concurrent chemoradiotherapy (details of eligibility are in Section 5.0). Each participant will undergo a pre-treatment (prior to chemoradiotherapy) whole-body PET scan, and both peak SUV and max SUV in the gross tumor volume will be calculated and recorded. Participants will then undergo chemoradiation. Participants on other prospective treatment studies will be treated as per the schema of that particular study. Participants not enrolled on other prospective treatment studies will be treated with conventional radiotherapy and concurrent chemotherapy consisting of platinum (cisplatin or carboplatin) plus second non-platinum, non-gemcitabine drug (e.g. etoposide, vinblastine, vinorelbine, paclitaxel, or docetaxel). Approximately 14 weeks (12 to 16 weeks) after the completion of definitive chemoradiation, participants will undergo a follow-up whole-body FDG-PET scan. Again, both peak SUV and max SUV in the gross tumor volume will be calculated and recorded. Participants will then be followed for long-term outcome. Correlation between the PET findings and clinical outcome will be performed by ACRIN as outlined in Section 15.0.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 Locally Advanced Non-small Cell Lung Carcinoma: Standard Treatment

Most patients with clinical Stage III non-small cell lung carcinoma (NSCLC) have technically unresectable disease, and many also harbor occult distant metastatic disease. For decades, thoracic radiotherapy (XRT) has been the conventional treatment for these patients, resulting in approximately 5-10% long-term survival with thoracic radiotherapy alone.¹⁻⁴ Since 1991, however, there have been at least 6 other trials in support of the hypothesis that combined modality

therapy improves survival over XRT alone.⁵⁻⁹ Several meta-analyses have been published that document the efficacy of chemotherapy.^{10,11} Highly influential organizations, including the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN), have issued consensus statements that chemoradiotherapy is the standard of care for relatively fit patients with Stage III NSCLC (except patients with malignant pleural/pericardial effusions who are generally treated as if they had Stage IV disease).¹² Despite these and other announcements, the cure rates remain poor.

One strategy to improve local control and survival is to increase radiation therapy dose intensity, as was successfully done in the CHART randomized trial¹³ and as is currently under investigation in dose-escalation studies using 3-D conformal radiotherapy.¹⁴⁻¹⁶ A second strategy to improve disease-free and overall survival is by increased use of systemic therapy, particularly concurrent chemoradiation and/or the integration of newer agents. This has shown promise in phase II non-randomized and Phase III studies.¹⁷⁻¹⁹

Treatment intensification is unlikely to work for all patients and could subject many patients to unnecessarily toxic and/or expensive therapies. For example, patients who are thought to have Clinical Stage III disease but actually have macroscopic distant metastases are unlikely to benefit from intensive thoracic radiotherapy but may be appropriate for systemic therapy with or without subsequent palliative-dose XRT. In contrast, patients whose disease can be well localized to a modest-sized volume might be excellent candidates for high-dose XRT (+/- modest dose “sensitizing” chemotherapy) and may be harmed by delaying XRT in order to deliver systemic therapy first.

2.2 Image-guided Treatment Planning and Assessment of Response

Several RTOG studies in the 1970s established 60 Gy in 6 weeks to large fields (2 Gy once daily) as the standard dose for NSCLC.^{4,20} These sizable fields have been considered necessary because of the sub-optimal ability of current imaging tests to identify the precise location(s) of tumor, and there is the suggestion that larger fields with better coverage of regional nodes might improve outcome.²¹ It is hypothesized that with the large fields used in this technique, there is little room for dose escalation or for minimization of toxicity.²² The utilization of “involved-field” radiotherapy has become a principle of most series of dose-escalated conformal XRT.^{14,23,24} With these high technology, high-dose techniques, optimal identification of the tumor location is critical.

An additional problem in the management of NSCLC is the difficulty in scoring local control and response to radiotherapy-based treatment using conventional imaging tests. While local control rates as defined by chest radiography (CXR) and physical examination are approximately 50%, when local control is rigorously assessed (e.g. via post-XRT bronchoscopy), true local control is probably significantly less than 50% for patients treated with non-surgical therapy.^{5,25,26} Although concurrent chemoradiotherapy regimens result in response rates as high as 70-80% (based on follow-up computed tomography [CT] scans),^{18,27,28,29} median survival in most series remains under two years.

2.3 FDG-PET Scanning in NSCLC

There is a clear need for improved imaging tests for the diagnosis, staging, treatment planning, and follow-up of NSCLC. The conventional imaging test for the past 20 years has been the chest CT scan (usually including the liver and adrenal glands). CT scans have at best modest sensitivity and specificity for the staging of NSCLC, particularly with regard to mediastinal lymph nodes.³⁰

Chest magnetic resonance imaging (MRI) scans have not shown an advantage over CT scanning.³¹ In contrast, positron-emission-tomography (PET) scanning with the glucose analogue F-18 fluorodeoxyglucose (FDG) appears to have better sensitivity and specificity than CT^{32,33} and may improve the staging of NSCLC.³⁴ A meta-analysis showed that the sensitivity and specificity for mediastinal nodal disease is approximately 79% and 91% for PET, compared with 60% and 77% for CT.³²

The utility of FDG-PET for NSCLC has been confirmed in several large surgical studies of preoperative staging.^{35,36} The results of these earlier studies have been confirmed in a recently completed large-scale U.S. cooperative group study conducted by the American College of Surgeons' Oncology Group (ACOSOG).⁵⁷

There have been fewer studies assessing PET scan for patients slated for non-surgical (XRT-based) treatment, and no cooperative group studies. This is at least partly because it is far more difficult to study PET in this setting, since non-surgical patients do not routinely undergo thoracotomy or other invasive studies to confirm (or dispute) the PET findings. Long-term follow-up of the patients is thus the only accurate way to assess the utility of PET. A series of studies from Australia shows that pre-radiotherapy PET scan findings correlate strongly with 2- and 3-year survival.³⁷⁻³⁹ Furthermore, in the study of 153 patients with unresectable NSCLC, 18% were found by PET to have distant metastases at presentation.⁴⁰

One critique of the Australian studies of PET and radiotherapy is the authors' reliance on qualitative analysis of the PET images, rather than on a more objective PET feature. In other centers, a semi-quantitative measure of FDG uptake within tumors, the standardized uptake value (SUV), has been widely studied and correlated with prognosis. The SUV is a relatively simple, easily reproducible measure of the FDG uptake within a tumor: the SUV is the ratio of the decay-corrected concentration of FDG within the tumor ($\mu\text{Ci/g}$) to the average concentration of FDG in the body (i.e. the administered activity divided by the body weight). The SUV of the primary tumor has been shown to correlate with prognosis in NSCLC.⁴¹

2.4 Significance of the Current Study

In addition to serving as a pre-treatment prognostic marker, post-treatment PET-SUV may be a better method of assessing response to XRT than CT scan alone.^{42,43 44,45} Rosenzweig et al. from Memorial Sloan-Kettering Cancer Center studied PET scans obtained approximately four months after definitive conformal XRT, showing that patients with a post-XRT SUV < 3.5 had a local control rate of 83%, compared with 23% for patients with an SUV > 3.5.⁴⁴ This study and similar studies by other investigators have been relatively small in size, however, and from single institution pilot series. Before post-treatment PET scans can be used as a method of "triage" for patients to receive additional therapies and before PET-response can be used as an early surrogate marker for the efficacy of new combined modality regimens, validation in a large study is necessary. In particular, the validity of using SUV as a quantitative marker of tumor activity should be demonstrated.

A final potential role for FDG-PET in the non-surgical management of NSCLC involves its use for radiation therapy treatment planning. Preliminary studies have shown significant alteration of the CT-based XRT target volume with the incorporation of FDG-PET findings.⁴⁶⁻⁴⁹ The XRT target volume may increase via PET identification of malignant nodes or tumor satellites unrecognized by CT scan.⁴⁶ Conversely, the target volume may be decreased by PET distinguishing between

“active” tumor and post-obstructive atelectasis.⁴⁷ There is also the suggestion that PET scanning decreases interobserver variation in the definition of target volumes for radiotherapy; in one study, interobserver variation in radiation oncologists’ definition of gross tumor was decreased in 23 of 30 cases.⁵⁰ There is a need, however, to confirm this and the other potential roles of PET described above in a large cooperative group study.

It is expected that this study will confirm some or many of the findings with regard to PET scanning for Stage III lung cancer, as described above. However, scientific studies to determine the mechanisms and translational implications of abnormal glucose metabolism in lung cancer are also necessary. Presumably, NSCLC is easily seen on FDG-PET images because it accumulates large amounts of glucose from the circulation for its metabolic function, using GLUT glucose transport proteins⁵¹ necessary for the malignant phenotype. In addition, there is the suggestion that increased FDG uptake on PET images correlates with conventional tissue markers of tumor aggressiveness,⁵² markers of hypoxia/angiogenesis, and/or molecular markers of high proliferation, such as Ki-67.⁵³ Overexpression of molecular markers of tumor biology in common solid tumors such as NSCLC may be associated with PET findings and/or clinical outcome, thus providing a new avenue for targeted therapies.

3.0 SPECIFIC AIMS

3.1 Primary Aim

To evaluate the ability of peak standardized uptake value (SUV) for FDG obtained at each institution **shortly after** definitive chemoradiation (post-treatment) to predict long-term survival in inoperable Stage II/III NSCLC.

3.2 Secondary Aims

- 3.2.1** To evaluate the ability of max SUV for FDG obtained at each institution **shortly after** definitive chemoradiation (post-treatment) to predict long-term survival in inoperable Stage II/III NSCLC.
- 3.2.2** To evaluate the ability of peak SUV and max SUV obtained at each institution **shortly after** definitive chemoradiation (post-treatment) to predict local control in inoperable Stage II/III NSCLC.
- 3.2.3** To evaluate the ability of peak SUV and max SUV obtained at each institution **prior to** definitive chemoradiation (pre-treatment) to predict long-term survival and local control in inoperable Stage II/III NSCLC.
- 3.2.4** To estimate the reliability of measuring post-treatment peak SUV and max SUV between the institution and a central review facility (see Section 11.3.2).
- 3.2.5** To estimate the reliability of measuring pre-treatment peak SUV and max SUV between the institution and a central review facility.
- 3.2.6** To estimate the percentage of patients with inoperable stage II/III NSCLC by conventional (non-PET) imaging who are upstaged, especially to Stage IV, after PET (+ confirmatory studies).
- 3.2.7** To estimate the reliability of qualitative interpretation of post-treatment PET (i.e., PET-defined response to therapy) between the institution and a central review facility (see Section 11.3.2).

- 3.2.8** To estimate the prognostic value of qualitative interpretations of post-treatment PET (i.e., PET-defined response to therapy) made at the institution and made at a central review facility (see Section 11.3.2).
- 3.2.9** To **explore** key differences between stages IIB/IIIA and stage IIIB with respect to peak SUV, max SUV, local control, and survival.
- 3.2.10** To collect tissue samples from patients treated in this study and estimate the correlation between immunohistochemical expression of Ki-67 (oncoprotein marker of cellular proliferation) and both peak and max pre-treatment PET-SUV measurement.
- 3.2.11** To explore the association between Ki-67 expression and overall survival.

4.0 STUDY OVERVIEW

This is a non-randomized study to determine the utility of pre- and post-treatment FDG-PET after definitive chemoradiation for locally advanced, inoperable non-small cell lung carcinoma (NSCLC). The primary aim is to determine the relationship between the peak SUV on a post-treatment PET scan performed approximately 3 months after therapy and long-term survival. Several other secondary endpoints related to the pre-treatment and post-treatment PET results will also be analyzed, and these are summarized in Section 3.2. Participants will be accrued over the course of two years. All participants will be followed for outcomes for 3 years beyond the end of the accrual period.

Eligible patients are those with Stage III (or medically inoperable Stage IIB) NSCLC who are not surgical candidates and are planned for definitive chemoradiation (radiotherapy \geq 60 Gy and chemotherapy to include concurrent platinum-based therapy).

These patients must have a good performance status (Zubrod 0-1) and must have a negative conventional distant-metastatic workup.

Participants will undergo a pre-treatment whole-body PET scan at an ACRIN-qualified facility according to the criteria of this protocol. This PET scan may be done before registration (as long as it is within 6 weeks) but it is strongly encouraged that registration to this study be done before this first PET scan. Participants will then undergo their definitive treatment. Participants who are on other, treatment-oriented clinical trials will be treated as per their treatment trial. Participants not on other treatment trials must be planned to receive 60+ Gy thoracic radiotherapy and concurrent chemotherapy (which must consist of a platin [cisplatin or carboplatin] and a second non-platin, non-gemcitabine drug). Participants may receive adjuvant chemotherapy after radiotherapy for up to three months after the completion of XRT. The post-treatment PET scan will be performed approximately 14 weeks (+/- 2 weeks) after the completion of XRT (at least 4 weeks after the end of adjuvant chemo if given). The post-treatment PET will be done at the same ACRIN-approved facility as the pre-treatment PET. Participants will then be followed for survival and patterns of failure.

5.0 PARTICIPANT SELECTION

Participants treated on any Phase II/III prospective treatment chemoradiation NSCLC trial will be automatically eligible for this study. In addition, selected patients not treated on a prospective treatment NSCLC trial will also be eligible if they meet all of the eligibility requirements described below.

5.1 Inclusion Criteria

- 5.1.1** Pathologically confirmed non-small cell lung carcinoma (NSCLC), exclusive of the diffuse bronchoalveolar subtype of NSCLC.
- 5.1.2** Clinical Stage IIB or III disease based on history, physical examination, laboratory, and conventional imaging tests, in accordance with 1997 AJCC staging criteria. The following **MINIMUM** workup is required to be eligible for this study:
 - 5.1.2.1** History/physical examination within 6 weeks prior to registration.
 - 5.1.2.2** Laboratory testing consisting at minimum CBC, glucose and liver-function tests (which must include at minimum alkaline phosphatase) within 4 weeks of registration.
 - 5.1.2.3** CT scan of the chest and upper abdomen (to include liver and adrenal glands) within 6 weeks, assuming there is no significant clinical change in the patient's condition. If there has been a significant clinical change in the patient's condition after this staging CT, a new chest CT scan must be obtained prior to registration on study.
 - 5.1.2.4** Head CT or MRI within 8 weeks, assuming the patient has no abnormalities on neurologic exam. If the neurologic exam becomes abnormal following this staging CT/MRI, a new head CT or MRI must be obtained prior to registration on study.
 - 5.1.2.5** Bone scan within 8 weeks, only if the patient has focal bone pain and/or other signs or symptoms suspicious for signs of bone metastases, such as alkaline phosphatase elevation.
- 5.1.3** Zubrod (ECOG) performance status 0 or 1 and medical suitability for early concurrent chemoradiotherapy including XRT dose ≥ 60 Gy.
- 5.1.4** Age ≥ 18 .
- 5.1.5** Women of childbearing potential must not be pregnant and all participants must use medically appropriate contraception if sexually active.
- 5.1.6** Study-specific informed consent.
- 5.1.7** Participants may be treated on other prospective treatment protocols of combined modality therapy for NSCLC, or they may be treated off protocol with standard concurrent chemoradiotherapy as described in Sections 12 and 13. NOTE: If study participant is receiving treatment on an RTOG clinical trial, eligibility criteria must be met for both the clinical trial and ACRIN 6668/RTOG 0235.
- 5.1.8** Able to tolerate PET imaging required by protocol, to be performed at an ACRIN-qualified facility (see Appendix III regarding ACRIN qualifications) and in compliance with protocol specifications, including ability to calculate SUV data (see Appendix IV regarding detailed PET specifications).

5.1.8.1 The initial PET scan may be done before registration (**as long as it is within 6 weeks and in compliance with protocol specifications**), but it is strongly encouraged that patients who have had a previous PET undergo an additional re-staging PET after registration.

5.2 Exclusion Criteria

5.2.1 Small cell carcinoma histology.

5.2.2 Stage IV disease (by physical examination, cross-sectional imaging tests such as CT or MRI, and/or bone scintigraphy). Note that patients with evidence of Stage IV disease by PET are still eligible **if** the findings cannot be confirmed by other means **and if** the physicians still plan to proceed with definitive chemoradiation. Patients with one or more very small pulmonary nodules visualized on CT scan that are remote from the primary tumor, less than 6 mm, indeterminate for lung-to-lung metastases and too small/deep to safely biopsy may still be enrolled on this trial if the physicians still plan to proceed with definitive chemoradiation.

5.2.3 Prior thoracic radiotherapy.

5.2.4 Poorly controlled diabetes (defined as fasting glucose level > 200 mg/dl) despite medications

5.2.5 Prior malignancy other than basal/squamous skin cancer, carcinoma in situ, or other cancer from which the participant has been disease free for less than 3 years.

5.2.6 Pregnancy or participants of reproductive potential who are sexually active and not willing/able to use medically appropriate contraception.

5.2.7 Anticipated use of adjuvant chemotherapy and/or biologic therapy beyond 16 weeks after the completion of radiotherapy.

5.2.8 Planned for definitive surgical resection.

6.0 SITE SELECTION

6.1 Institution Requirements

The potential participants for this study are RTOG member sites and ACRIN participating institutions that meet qualifications for participating in this study. Traditionally, about 40% of RTOG's 250 member sites will open a trial. To qualify for ACRIN participation, all RTOG and ACRIN sites must review the Institution Participating Guidelines (Appendix V) and the Protocol-Specific Application (see Appendix VII for more information). All institutions must complete a Protocol-Specific Application (PSA) and have the PET scanner approved prior to the institution participating in the study (see Section 6.1.1). Detailed information for PET Credentialing and the Protocol-Specific Application can be accessed at www.acrin.org/6668_protocol.aspx.

Participating RTOG institutions should **not** submit regulatory documentation (e.g., IRB approval) to CTSU for this protocol. **Submit all regulatory documentation to ACRIN Headquarters via fax: 215-717-0936.**

6.1.1 PET Credentialing

To participate in this study, the site must be able to conform to all of the criteria described in ACRIN website, www.acrin.org/6668_protocol.aspx. This must be confirmed by a credentialing process from ACRIN website, www.acrin.org/6668_protocol.aspx. This

process includes submission of test images to ACRIN. The test images will be reviewed by one or more of the study investigators for compliance. Only after approval by ACRIN can an institution enroll participants on this study. Centers that have received PET approval for other ACRIN studies may be eligible for expedited credentialing after discussion with the study investigators.

6.1.2 *Radiation Therapy*

Participants enrolled in this study must receive their radiation therapy at an RTOG member institution. At the time of registration this will be verified by requesting the RTOG institution number where the participant will be treated. That RTOG institution will then be responsible for providing radiotherapy simulation films to their local ACRIN investigators for submission to ACRIN Headquarters. (In some institutions, RTOG investigators may submit simulation films directly to ACRIN.)

6.2 IRB Approval and Informed Consent

All institutions must have study-specific IRB approval. ACRIN/PET centers that are located within a hospital are expected to obtain approval from that hospital's IRB. Freestanding ACRIN/PET centers may obtain approval from the IRB that has jurisdiction over that ACRIN/PET center's RTOG partner, which will typically be the hospital where radiation therapy is given and/or where the radiation oncologist investigator is responsible for inpatient consultations.

RAs must follow OHRP-approved consent procedures, as well as those set by the Institutional Review Board (IRB) at the institution. A copy of IRB approval, the sample institutional study-specific consent form, and the institution's federal wide assurance information must be on file at ACRIN Headquarters (fax 215-717-0936) prior to registering the first participant.

6.3 Accrual Goals

The ACRIN Biostatistics and Data Management Center (BDMC) will monitor participant accrual. Target accrual is 250 total participants, with at least 75 Stage IIB/IIIA and at least 75 Stage IIIB. During the first year, accrual will be reviewed monthly with the intention of discovering and resolving any barriers. The ACRIN Steering Committee will be notified if total accrual is less than the number specified in the table below. Due to the various issues involved in ramping up the study, in particular IRB approvals, very little to no accrual is expected in the first six months after the study opens. However, particular attention will be paid to accrual at 9, 12, and 15 months to determine if the study is on course and if the projected accrual goals can be met. Accrual information will be presented to the ACRIN Data Safety and Monitoring Committee (DSMC) at regularly scheduled meetings thereof; the DSMC may, at its discretion, re-evaluate the study with respect to feasibility.

Months since activation	Required cumulative accrual	Required accrual, each of IIB/IIIA and IIIB
7	7	2
8	14	4
9	21	6
10	28	8
11	35	10
12	42	13
13	49	15

14	56	17
15	63	19
16	69	21
17	76	23
18	83	25

In order to ensure that at least 75 participants with clinical stage IIB/IIIA and at least 75 with clinical stage IIIB disease are accrued, the ACRIN BDMC will monitor the number of participants in these groups. If the number in either group falls below the number specified in the table above, the trial team will consider appropriate corrective action.

In order to ensure that the assumptions used in the sample size computations are not substantially violated, the ACRIN BDMC will monitor the proportion of participants on whom post-treatment SUVs are obtained (expect 80% of number enrolled, see Section 15.5), the proportion of evaluable participants (expect 68% of number enrolled, see Section 15.5), and the proportion of evaluable participants with post-treatment peak SUV ≤ 3.5 (expect 45% of evaluable participants, see Section 15.5) monthly throughout the trial. If at any point in time a 95% confidence interval (CI) for the proportion of evaluable participants lies entirely below 68%, reasons for this will be discussed and possible remedies will be considered; the study may be re-evaluated, in light of the expected results of any proposed remedies, for necessary sample size and anticipated extension of the accrual period. If this CI lies entirely above 68%, a revised smaller sample size to maintain desired power may be calculated. If at any point in time a 95% CI for the proportion of evaluable participants with post-treatment peak SUV ≤ 3.5 lies entirely below or entirely above 45%, a revised sample size and its anticipated effect on the accrual period will be calculated. The ACRIN DSMC will be notified of these results at its next regularly scheduled meeting, and may at their discretion re-evaluate the study sample size and/or feasibility.

In order to ensure that the assumption about overall survival used in the sample size computations is not substantially violated, the ACRIN BDMC will estimate the overall proportion of participants surviving at one year. This estimation will occur monthly, beginning when 188 participants have been accrued (approximately 6 months before the end of the planned accrual period). Based on 40% 2-year survival (see Section 15.5), 1-year survival is expected to be 63%. If a 95% CI for this proportion lies entirely below or entirely above 63%, a revised sample size and its anticipated effect on the accrual period will be calculated. The ACRIN DSMC will be notified of these results at its next regularly scheduled meeting, and may at their discretion re-evaluate the study sample size and/or feasibility. Note that this is not an interim analysis, as survival within level of peak SUV will not be evaluated.

7.0 ONLINE REGISTRATION SYSTEM

Patients can be registered only after eligibility criteria for the study are met. An institution can register the patient by logging onto the ACRIN web site, www.acrin.org, and selecting the link for Data Center login, then choosing the ACRIN protocols link (see Section 7.1). Once the patient is registered, case-specific data will be sent to RTOG Headquarters so that the institution is reimbursed.

7.1 Using the Online Registration System

Once the investigator-designated research staff (i.e. the Research Associate [RA]) has completed the eligibility checklist (Appendix II) and the participant has been found to be eligible, the participant may be consented. Upon obtaining a signed informed consent form, the information of

the study participant will be registered by logging onto the ACRIN web site (www.acrin.org), which is available 24 hours a day, 7 days a week.

7.2 Unsuccessful Registrations

7.2.1 ACRIN and protocol-specific requirements for institution participation are maintained within the administrative database. The protocol specific attributes are then interfaced with the web application for on-line verification of site participation acceptance. If the institution has not met all the regulatory requirements based on the required attributions within the database, a screen that includes a brief explanation of the failure to gain access to the registration screens is projected. If during the completion of the eligibility questions a participant is deemed ineligible based on a response, a message box appears to instruct the research staff to contact the Data Management Center.

7.2.2 In the unlikely event that the ACRIN web registration site is not accessible, participating sites may still register a participant by faxing the completed eligibility checklist to the DMC at the ACRIN (215-717-0936, ATTN: PARTICIPANT REGISTRATION). ACRIN staff will fax a response to the registering site with the confirmation of registration and participant case number as soon as possible.

8.0 DATA COLLECTION AND MANAGEMENT

8.1 General

8.1.1 The ACRIN web address is www.acrin.org.

8.1.2 Data collection and management will be performed by the Biostatistics and Data Management Center (BDMC) of ACRIN under the direction of Dr. Constantine Gatsonis. The Biostatistics Center (BC) is located at Center for Statistical Sciences at Brown University in Providence, RI, and the Data Management Center (DMC) is located at the American College of Radiology's Data Management Department in Philadelphia.

8.1.3 Participant enrollment and data collection occurs through a series of programmed screens accessed through the ACRIN web site to register/randomize participants, collect participant data, and maintain calendars of data submissions for each participant. By using the World Wide Web, ACRIN has made participant registration, data entry, and updated calendar information available to clinical sites 24 hours a day, seven days a week. Each successful case registration is confirmed through receipt of an e-mail containing a registration/randomization confirmation and a case specific calendar identifying timelines for data and image submission. If the confirmation e-mail is not received, the enrolling person should contact the Data Management Center before attempting a re-registration.

8.2 Clinical Data Submission

8.2.1 Upon successful participant registration, a confirmation e-mail containing the registration and case specific calendar is sent to the research staff enrolling the participant via the web. In addition, the investigator-designated research staff may download the participant specific data submission calendar, which lists all forms and designated reports required by protocol, along with the form due dates at the DMC. These calendars will be updated as the study proceeds to reflect data that have been received, reply deadlines 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. Updated calendars for each

participant can be obtained 24 hours a day from the ACRIN website. The research associate may use the calendar as a case management tool for data submission and follow-up scheduling.

- 8.2.2** The investigative site is required to submit data according to protocol as detailed on each participant's calendar, as long as the case status is designated as open/alive or until the study is terminated. The case is closed when all data have been received and reviewed, and no outstanding data query exists for the case.
- 8.2.3** To submit data via the ACRIN website, the appropriate investigator-designated research staff will log onto the ACRIN web site and supply the pre-assigned user name and password. Case report forms will be available on the web site through a series of links. Each web form is separated into modules; each module must be completed sequentially in order for the internal programming to be accurate. 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 missing data, data that are out of range, and data that are 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. They must be corrected before the form is transmitted to the DMC. 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 Submission" button is depressed.
- 8.2.4** Once data entry of a form is complete, and the summary form reviewed for completeness and accuracy, the investigator or the research staff presses the "Complete Form Submission" 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 completed 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 Data Management Center for resolution of the submission.
- 8.2.5** If a temporary problem prevents access to the Internet, all sites are notified of the event and estimated down time through an ACRIN broadcast message. The investigative site should wait until access is restored to submit data. The site RA or investigator should notify the DMC of the problem and the DMC will give an estimated time when access will be restored. If access will be unavailable for an extended period, sites must seek another Internet Service Provider (ISP). On a short-term basis, the ACRIN can serve as an ISP.

8.3 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 will be controlled by a sequence of identification codes and passwords.

8.4 Electronic Data Management

- 8.4.1** 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 Brown BC and the DMC. The logic checks performed on the data at this point are more comprehensive than those built into the web-based data entry screens. They include checking that answers are logical, based on data entered earlier in the current form and the more thorough checks. Data elements that fail validation are followed up by the DMC. The validation program generated by BC produces a log of errors, which is sent to the DMC for resolution. The program is frequently updated to incorporate exceptions to rules so that subsequent validity checks minimize the time the DMC needs to spend resolving problems. Additional data review will take place once the data is transferred to the BC. The BC will run thorough cross-form validations, frequency distributions to look for unexpected patterns in data, and other summaries needed for study monitoring. Any errors found at the BC will be reported to the DMC for resolution. All BDMC communication with the participating sites is normally done through the DMC.
- 8.4.2** If checks at DMC or BC detect missing or problematic data, the DMC sends a Request for Information (Z1 query letter) to the site RA or investigator specifying the problem and requesting clarification. The DMC updates the participant's data submission calendar with the due date for the site RA or investigator's response.

8.5 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. Distributed at intervals via the electronic mail system directly to both the RA and the investigator at each site, this report lists data items (e.g. forms, reports, and images) that are delinquent and those that will be due before the next report date. 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 Due Forms Report may be sent on an as needed basis in addition to past due reports. The site investigator or research associate may use the Forms Due and Future Due Reports as a case management tool.

8.6 Data Quality Assurance

- 8.6.1** The 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 of the DMC. The transfer of data between the DMC and the BC has 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 DMC for resolution, since only the DMC can correct the data file. No changes to the data will be made at the BC.
- 8.6.2** A goal of the monitoring of data is 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 Biostatistical and Data Management Center (BDMC) will apprise the ACRIN Headquarters and the site of the problem, and work with the site, along with ACRIN

Protocol Development and Regulatory Compliance Department, until the problem has been resolved. If the BDMC, along with the Audit Group, cannot find a resolution to the problem, it will be brought to the Steering Committee for further discussion and resolution.

- 8.6.3** In addition, the ACRIN Quality Assurance (QA) Monitor will review case report forms and source documents at several different time points during accrual period on selected study participants enrolled at each site. In addition, the QA Monitor will review the initial regulatory documents. This monitoring process is to ensure compliance and to provide clarification in completion of the case report forms in order to minimize any inconsistencies or misunderstandings.

8.7 Data Submission and Adverse Event Reporting for RTOG Institutions

Participating RTOG institutions will submit data as specified in Section 8.0 and Adverse Events as specified in Section 16.0. Clinical data and adverse events are not submitted to RTOG Headquarters.

9.0 DATA COLLECTION FORMS

Case report forms for data collection for this study are available on the ACRIN 6668 protocol web site, www.acrin.org/6668_protocol.aspx. Refer to the form completion guidelines for information regarding form completion and form submission.

10.0 IMAGE SUBMISSION

10.1 FTP Transfer

Digitally generated image files in DICOM v3.0 and scanned film diagnostic images can be transmitted to the ACRIN Image Management Center (IMC) via FTP directly to the image archive. For the PET imaging, processes are being put in place to collect the vendor specific image files. For further assistance in utilizing the electronic image submission option or for questions regarding image transfer, contact Cyndi Fenerty (cfenerty@phila.acr.org; 215-940-8863) or Anthony Levering (alevering@phila.acr.org).

10.1.1 Removal of Confidential Participant Information

If DICOM is being used, please note that the header record on DICOM formatted image data, which often contains information identifying the participant by name, **MUST** be scrubbed before the image is transferred. This involves replacing the Participant Name tag with the ACRIN Institution ID or number, replacing Participant ID tag with the ACRIN case number, and putting the study number into the Other Participant ID tag. This can be performed using a customized software program or using a program available from ACRIN. Contact Cyndi Fenerty (cfenerty@phila.acr.org) or Anthony Levering (alevering@phila.acr.org).

10.1.2 PET Data Submission Instructions

The data should consist of three volume or multi-slice files as follows: 1. Transmission scan; 2. Emission scan with attenuation correction; and 3. Emission scan without attenuation correction.

For further assistance in utilizing the electronic image submission option or for questions regarding image transfer, contact Cyndi Fenerty (cfenerty@phila.acr.org; 215-940-8863), or Anthony Levering (alevering@phila.acr.org; 215-574-3244).

10.2 CD Transfer

In the event that either DICOM capability or transfer of scrubbed image headers is not available, images may also be sent on a CD or other electronic medium for the ACRIN IMC to transfer to the image archive. Please contact ACRIN prior to sending the media to confirm compatibility, particularly before your first case to Cyndi Fenerty (cfenerty@phila.acr.org; 215-940-8863).

10.2.1 PET Data Submission Instructions

The data should consist of three volume or multi-slice files as follows: 1. Transmission scan; 2. Emission scan with attenuation correction; and 3. Emission scan without attenuation correction.

10.3 Plain Film Images

Plain film images for the PET scans are not acceptable for this study. Plain film images for submission of other images (CT scans, radiotherapy simulation films, and port films) are acceptable.

Where applicable (CT scans, radiotherapy simulation films), plain film images may be sent via mail for digitization and subsequent entry to the image archive. All media and film will be retained by the ACRIN IMC unless otherwise requested, and return packaging and postage is provided.

10.4 Images stored in the ACRIN IMC image archive will then be routed to the Core PET-NSCLC facility at ACRIN for central review analysis.

10.5 ACRIN Qualification

An institution must be certified for PET by ACRIN prior to registering participants. The process for qualification and accreditation is outlined in ACRIN website, www.acrin.org/6668_protocol.aspx.

10.6 Quality Control

A review of the first two cases will be performed in order to ascertain the quality of image processing at the contributing institutions for adequate quality. Computed Tomography and PET images from the first two cases accrued from each institution will be sent to the ACRIN image archive in Philadelphia as per Section 10.1. The CT image studies will be reviewed by Dr. Mitchell Machtay at the ACRIN Image Core Laboratory (AICL) in Philadelphia. After that time, 10% of all imaging studies will be reviewed for quality control purposes.

In cases of suboptimal quality ratings, the study in question will be reviewed and a decision will be made regarding eligibility for the study.

11.0 DIAGNOSTIC EVALUATION OF STUDY PARTICIPANTS

11.1 Initial Evaluation of Patients (in addition to the pre-treatment PET scan)

11.1.1 History and physical examination (mandatory for registration to study as per section 5.1.2.1).

11.1.2 Diagnostic CT scan of the chest and upper abdomen to include liver and adrenal glands (mandatory for registration to study as per Section 5.1.2.3).

11.1.2.1 Diagnostic Chest CT Technique

The chest CT scan will include 0.5 cm or less slice thickness of the thorax and gross tumor and must use helical and/or multislice technology. IV contrast will be used unless there is a medical contraindication, such as contrast allergy. (Note that this CT scan is in addition to any CT scan[s] done for radiation therapy dosimetry planning and is in addition to the CT done as part of a conjoint PET-CT study).

11.1.3 Whole-body bone scan, if the patient has skeletal symptoms suspicious for metastases and/or elevated alkaline phosphatase.

11.1.4 Head CT or MRI (mandatory for registration to study as per Section 5.1.2.4). For head CT, IV contrast will be used unless there is a medical contraindication. If MRI is used, IV contrast is not mandatory.

11.1.5 Laboratory testing to include at minimum CBC, glucose, and alkaline phosphatase (mandatory for registration to study as per Section 5.1.2.2).

11.1.5.1 Additional recommended laboratory testing: chemistry battery (electrolytes, calcium, glucose, liver function tests).

11.1.6 Cardiopulmonary evaluation (highly recommended though not mandatory): EKG and pulmonary function tests (spirometry and DLCO).

11.2 Study (Initial) PET Scan

The initial PET scan may be done before registration (as long as it is within 6 weeks), but it is strongly encouraged that patients who have had a previous PET undergo an additional re-staging PET after registration. In either scenario, the PET must be performed or have been performed as per the criteria described below.

11.2.1 PET Equipment (Refer to ACRIN website, www.acrin.org/6668_protocol.aspx)

A dedicated PET scan unit or hybrid PET/CT scanner is mandatory. Sodium Iodide (NaI) instruments will not be eligible in this study. The PET 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. For questions regarding whether the PET scanner to be used is in compliance with this protocol, contact one of the Nuclear Medicine Study PIs (Dr. Barry Siegel, Dr. Abass Alavi or Dr. Janet S. Reddin; see cover sheet for contact information).

11.2.2 Participant/FDG Preparation

Participants must fast for minimum 4 hours prior to the injection of FDG for the PET scan. Blood glucose will be measured within 2 hours of PET scan and must be ≤ 200 mg/dl. The blood glucose level must be recorded prior to the injection of FDG. FDG will be synthesized and prepared in accordance with the institution's standard procedures or obtained from a commercial supplier.

11.2.3 FDG Injection

The administered activity of FDG should be based on the recommendation of the manufacturer of the specific PET scanner being used for the study. For facilities using a

dedicated BGO, LSO, or GSO PET system, the recommended FDG dose is 0.14-0.21 mCi/kg. The actual FDG dose should be 10-20 mCi. A dose at the higher end of the range is recommended, if feasible, with appropriate reduction in the per kilogram dose for heavier patients (in accordance with the manufacturer's recommendation). Dedicated NaI systems will not be eligible for this study.

11.2.4 *PET Imaging*

Emission imaging will be started 50-70 minutes after FDG injection. The participant will empty his/her bladder immediately before the acquisition of images. The participant will be scanned supine and should be done with arms up. To help with radiotherapy planning, it is encouraged that the scans be done in a position as closely approximating the radiation therapy treatment position as possible (the use of the participant's customized radiation therapy immobilization device during the PET scan would be optimal).

The scanned volume will be from the upper/mid-neck to the proximal femurs. A series of transmission scans (or a CT scan with a hybrid PET/CT scanner) will be performed (to account for tissue attenuation) in addition to emission scans. The duration of acquisition for emission data should be in accordance with the manufacturer's recommendations and the data must be corrected for scatter, random events, and dead-time losses using manufacturer's software. Bed positions should be overlapped to avoid large changes in sensitivity at the joints between the bed positions.

Institutions that ordinarily do so may perform a second PET acquisition scan approximately 30 minutes after the first (main) PET scan, in order to assist in qualitative interpretation of the PET. This 2nd timepoint imaging scan does not require any additional administration of FDG. This does not have to be a complete PET scan but may include only areas that had increased uptake on the first (main) PET scan. The second PET acquisition scan should only require an additional 10-15 minutes of scanning time.

11.2.5 *Post-PET Participant Care*

The participant will empty his/her bladder again immediately following PET imaging.

11.2.6 *Image Reconstruction and Analysis*

Image reconstruction will depend on the scanner manufacturer. We recommend an interactive reconstruction method with preference for OSEM reconstruction, 8 subsets, 2 iterations, followed by smoothing with a 6-mm 3D Gaussian kernel. Both visual/qualitative and quantitative (SUV) PET data analysis will be performed.

11.2.7 *Interpretation and Implications of PET Images for Distant Disease*

If there is evidence of M1 disease by PET scan, further evaluation needs to be performed, since a designation of metastatic disease usually has very serious implications for the participant. This is the responsibility of the treating institution. The following guidelines are recommended:

11.2.7.1 Any area on PET that is suspicious for M1 disease should be re-evaluated on the participant's previously performed CT scan. If a lesion is noted on the CT/MRI, biopsy should be performed if feasible. If the biopsy is positive, the participant should be treated as per the clinician's preference. If the biopsy is non-diagnostic, consideration should be given to repeat biopsy. If the biopsy is negative and/or

repeatedly non-diagnostic, it is recommended that the participant receive chemoradiation as described within this study.

11.2.7.2 If the areas on PET that are suspicious for M1 disease are not seen in retrospect on the previously performed CT scan, repeat CT (optimized for assessing the organ of concern) or MRI should be performed. MRI may be particularly useful for visualizing and further characterizing PET-positive abnormalities in the adrenal glands and/or bones. After repeat CT or MRI, reconsideration should be given to biopsy if feasible. If the biopsy is positive, the participant should be treated as per the clinician's preference. If the biopsy is non-diagnostic, consideration should be given to repeat biopsy. If the biopsy is negative and/or repeatedly non-diagnostic, it is recommended that the participant receive chemoradiation as described within this study.

11.2.7.3 If the areas on PET that are suspicious for M1 disease are not amenable to biopsy after review of all imaging tests, but the MRI and/or other scans are considered strongly positive, the participant should be considered to have unconfirmed M1 disease. In this situation, it is strongly recommended that the participant receive chemoradiation as described within this study.

11.2.8 *Interpretation and Implications of PET Images for Local-regional Disease*

Local-regional areas that are positive by PET will be included in the radiotherapy portals even if not positive by CT scan (see Section 12.2) unless in the judgment of the radiation oncologist this makes the radiotherapy portals excessively large (unsafe). If the radiation oncologist determines that the PET-defined target volume is too large for safe thoracic radiotherapy, the participant will be treated as per physician preference "off study." This treatment will typically consist of chemotherapy alone and/or palliative radiotherapy. The participant will not be considered evaluable for the primary endpoint of the study (post-chemoradiotherapy SUV analysis).

Local-regional areas that are equivocal by PET scan may or may not be included in the radiotherapy portals – the clinical judgment of the radiation oncologist will be used. However, the use of confirmatory imaging and/or pathologic studies such as thoracic MRI or bronchoscopy is encouraged. In some settings it may be appropriate to subject the participant to an invasive procedure (e.g. mediastinoscopy, thoracentesis, thoracoscopy) for optimal definition of the extent of local-regional disease. Both the core lab and the treating site will follow the same analysis and reading procedures, but only the treating site will make medical decisions and be responsible for follow-up of the patient based upon these readings.

11.2.9 *Determination of Standardized Uptake Value (SUV)*

For the purposes of this study, the relevant SUV's for calculation and reporting will be the "peak SUV" and "max SUV" within the primary gross tumor volume. These will be determined by the nuclear medicine physician visually identifying the region or regions on the PET images that qualitatively appear to have the most intense FDG uptake and that correspond to known tumor based on other data (such as CT scan). Both the peak SUV and the max SUV are to be calculated and reported because they each have advantages and disadvantages. Specifically, the peak SUV is less prone to "noise bias" than max SUV, and thus peak SUV will remain as the primary statistical endpoint of this protocol. However,

peak SUV is more difficult to measure, especially for some PET software systems and thus max SUV may have better inter-observer reliability. Max SUV will be a secondary endpoint of this protocol, as outlined in Section 3.

For peak SUV determination, a circular region of interest (ROI) 0.75 to 1.5 cm in diameter centered on the maximum-value pixel will be drawn, and the manufacturer's algorithm will be used to calculate the mean SUV within this ROI; this value will be reported as the peak SUV. Prints of the image and the SUV cursor or region of interest should be acquired and retained for source documentation.

For max SUV determination, an ROI incorporating the gross tumor volume will be identified by the nuclear medicine physician and the manufacturer's algorithm will be used to calculate the maximum SUV within this ROI. Prints of the image that includes the ROI should be acquired and retained for source documentation. If two or more regions of interest are analyzed, the one with the higher peak SUV will be reported for the purposes of this protocol. These procedures will be followed by both the local site and the core lab.

The SUV's obtained and used for the primary and the major secondary endpoints of this study as outlined in Section 3 will not be corrected for body-surface area or other measure of patient size/shape. We will, however, also collect patient height and weight data and will perform an exploratory analysis of SUV corrected for body-surface area and whether performing this correction provides more useful data than conventional, uncorrected SUV.

11.3 Post-treatment Study PET

The post-treatment PET scan is to be done according to the same specifications described in detail above (Section 11.2). The PET scan needs to be done on the same scanner (or, if this is not feasible, on the same model PET scanner) within the same ACRIN-qualified institution used for the pre-treatment PET.

The post-treatment PET scan will be done approximately 14 weeks after the completion of XRT (and at least 4 weeks after adjuvant chemotherapy, if given). It will be done no sooner than 12 weeks after the completion of radiotherapy in order to allow for partial resolution of post-treatment inflammatory effects that can cause false positive PET scan results.

11.3.1 Definition of Protocol Variation PET Scan

Per protocol: Post-treatment PET scan done according to the specifications of Section 11.2 and is done between 12 and 16 weeks after the completion of all radiotherapy.

Minor Variation: Any of the following will be considered a minor variation:

- Post-treatment PET scan done between 8 and 12 weeks after the completion of all radiotherapy.
- Post-treatment PET scan done between 16 and 20 weeks after the completion of all radiotherapy/chemotherapy.
- Post-treatment PET scan done 12-20 weeks after radiotherapy, but less than 4 weeks after adjuvant chemotherapy.
- Post-treatment PET scan done on a **different model** PET scanner from the pre-treatment PET (but still within the same ACRIN-qualified institution).

Major Variation: Any of the following will be considered a major variation (violation):

- Post-treatment PET scan done sooner than 8 weeks after the completion of radiotherapy.
- Post-treatment PET scan done later than 20 weeks after the completion of all radiotherapy/chemotherapy.
- Post-treatment PET scan done at a non-ACRIN-qualified institution.
- Post-treatment PET scan not done according to specifications of Section 11.2 (e.g. incorrect dosage of FDG, incorrect scan times).

11.3.2 *Interpretation and Implications of Qualitative Analysis of Post-treatment PET Scan*

The post-treatment PET scan should be interpreted together with the pre-treatment PET scan, a post-treatment CT scan, and knowledge of the irradiated volume and other relevant clinical information. An area or areas of concern for the development of metastatic disease or progressive local-regional disease should be further evaluated as described in Sections 11.2.7 and 11.2.8. These procedures will be followed by both the local site and the core lab.

With respect to metastatic disease, the post-treatment PET will be qualitatively analyzed and categorized using a 5-point scale: 1. Definitely no metastatic disease; 2. Probably no metastatic disease; 3. Indeterminate; 4. Probably metastatic disease; 5. Definitely metastatic disease.

Since it is extremely difficult to quantify the size of a lesion(s) by PET scan, the conventional RECIST criteria will not be used for the qualitative, non-SUV-based PET scan interpretation after chemoradiotherapy. Instead, the qualitative visual criteria from Mac Manus et al. will be utilized, as follows:

- (1) CR will be defined as no tumor FDG uptake in the tumor bed, or activity in the tumor bed similar to that in the mediastinum;
- (2) PR will be defined as appreciable reduction in intensity of tumor FDG uptake or tumor volume apparent to the nuclear medicine physician when pre- and post-treatment PET scans are displayed side by side; *
- (3) NR will be defined as no appreciable change in intensity of tumor FDG uptake or tumor volume between scans and no new sites of disease apparent to the nuclear medicine physician when pre- and post-treatment PET scans are displayed side by side; *
- (4) PD will be defined as appreciable increase in the intensity of tumor FDG uptake or volume of the tumor apparent to the nuclear medicine physician when pre- and post-treatment PET scans are displayed side by side. *

* For these determinations, the pre- and post-treatment PET scans must be analyzed using the same display techniques to provide a consistent intensity of background soft-tissue activity.⁵⁸

Peak SUV will be determined as for the pre-treatment PET scan (see Section 11.2.9).

11.4 Summary Table of Participant Evaluation

Note: Participants who are on another prospective treatment study will be followed according to the follow-up schema of their primary therapeutic study. For those participants not on another RTOG study, the following schema will be followed:

Procedure	Pre-Rx	Q1-2 weeks During Chemo-RT*	Within 12-16 weeks after radiotherapy	“Long term” Follow-up ^a
History and Physical Examination	X	X	X	X
Weight and KPS	X	X	X	X
Toxicity Evaluation		X	X	X
CBC, diff, platelets	X	X	X ^d	X ^d
Serum chemistry (see Section 5.1.2)	X	X	X ^d	X ^d
EKG	X ^d			X ^d
PFTs (Spirometry/DLCO)	X ^d			X ^d
Chest CT (including liver/adrenals)	X		X ^c	X ^b
PET scan	X		X ^c	X ^d
Other imaging studies as necessary (e.g. Head CT, Bone scan, etc.)	X		X ^d	X ^d
Pregnancy test (women of childbearing potential)	X ^e		X ^e	

* Participants should be seen by a radiation and/or medical oncologist at least once per week during radiotherapy. Documentation of physical exam, toxicity assessment, weight/performance status, and labwork is mandatory at least once every two weeks. Toward the end of radiotherapy (and for several weeks after radiotherapy finishes), more frequent visits may be needed because of acute toxicity.

- Follow-up Schedule: Participants should be seen at least q2 wks until resolution of acute toxicity to \leq Grade 2. Subsequent follow-up visits should be q3 mo. x 2 years, then q6 mo. x at least 1 year with the first follow-up visit to begin three (3) months post completion of treatment (or until this study has been terminated). Participants who are on another RTOG or other cooperative group study will be followed according to the follow-up schema of their primary therapeutic study.
- CXR's should be done with each follow-up in which a Chest CT has not been done. This is to assess for gross tumor progression, pneumonia, or other serious morbidity. Diagnostic quality thoracic CT scan is mandatory (not XRT planning CT scan).
- The post-treatment Chest CT and PET scan are mandatory and are the primary endpoint of this protocol. These should be done at approximately Week 14 (between Weeks 12 and 16) after the completion of radiotherapy (corresponding to approximately Week 21 after registration on-study); and, \geq 4 weeks after adjuvant chemotherapy. The post-treatment PET scan will be performed in accordance with Sections 11.2 and 11.3.
- As clinically indicated. Baseline and follow-up EKG, pulmonary function testing, laboratory tests are recommended in order to assist in accurate assessment of potential toxicity from chemoradiation.
- Women of childbearing potential must have a negative pregnancy test before undergoing the pre-treatment PET scan and before undergoing the post-treatment (follow-up) PET scan.

12.0 RADIATION THERAPY

12.1 Summary of Radiation Therapy

Participants treated on other prospective treatment NSCLC protocols will be treated as per those protocols. Participants not on other prospective treatment NSCLC protocols will be treated with conventional fractionation XRT (1.8-2.0 Gy per day) to a minimum dose of 60 Gy as described

below. This represents standard-of-care radiotherapy and is not a research component of this (PET scan) study, but radiotherapy specifications are outlined below for treating physicians' reference and assistance. These participants will also be treated with concurrent chemotherapy. There are no specific requirements on details of chemotherapy, except that concurrent platinum (cisplatin or carboplatin) plus a second non-platin non-gemcitabine drug is mandatory.

12.2 Radiation Treatment Planning

12.2.1 Target Planning CT

A target planning CT scan is required in order to define gross tumor volume (GTV), particularly for "off cord" radiation beam arrangements. The planning CT should include contiguous CT slices 3-5 mm in thickness through areas harboring GTV and 3-10 mm in thickness for other portions of the chest. IV contrast is suggested but not required as long as a previous diagnostic CT or MRI of the chest was done with IV contrast and available for correlation with the planning CT.

12.2.2 Dose/Volume Requirements (Initial Field)

Participants not treated on another prospective treatment protocol (particularly 3-D QA protocols such as RTOG L-0117) should be treated initially to a field that encompasses not only CT-based GTV, but also selected "elective" regional nodes, particularly the ipsilateral hilum. Treatment of the paratracheal nodes and/or subcarinal nodes to 5 cm below the carina is also appropriate. **Any area(s) considered grossly positive on PET scan will also be included in the field even if not involved by CT scan. Similarly, any area grossly positive for tumor on CT scan will be included in the field even if not involved by PET scan.**

- Minimum distance from the edge of GTV to block edge is 1.5 cm in the right-left and anterior-posterior dimensions and 2 cm in the superior-inferior dimensions (the superior-inferior margin is slightly greater because of breathing variation).
- Larger margins may be necessary depending on the quality of the planning CT scan(s) and external and internal immobilization.
- The ipsilateral supraclavicular nodes may be included for upper lobe lesions and/or bulky N2 disease.
- The inferior mediastinal nodes may be included for middle/lower lobe lesions and/or when subcarinal nodes are grossly involved.
- The contralateral hilum may be included when contralateral mediastinal and/or subcarinal nodes are grossly involved.
- The initial field/volume will be treated to 40-50 Gy, limiting the spinal cord dose at any point to 42 Gy – note that the AP-PA "on cord" prescription should thus be limited to about 40 Gy.

12.2.3 Dose/Volume Requirements (Conedown Field)

All participants will undergo one or more conedowns to reach a total dose to GTV (**including areas considered by the radiation oncologist to be positive on PET scan**) of at least 60 Gy. Any field arrangement may be used to reach this dose as long as normal tissue constraints are fulfilled. Minimum distance from the edge of GTV to block edge for the conedown field is 1 cm in the right-left and anterior-posterior dimensions; 1.5 cm in the

superior-inferior dimensions (because of breathing variation). Somewhat larger margins may be necessary depending on the quality of the planning CT scan(s) and external and internal immobilization.

12.3 Technical Delivery Factors

12.3.1 Beam Energy

Megavoltage energies are required, with minimum peak energy of 6MV. It is suggested that peak energy not exceed 10 MV.

12.3.2 Treatment Distance

Minimum source-axis distance (SAD) for SAD technique (recommended) is 100 cm. For skin-surface distance (SSD) technique, minimum SSD is 100 cm.

12.3.3 Blocking/Multileaf Collimation (MLC)

Customized blocks and/or MLC in all fields is generally indicated, particularly to assure that the normal tissue constraints of Section 12.4 are not exceeded. In the case of a large sloping contour, such as usually encountered when treating upper lobe tumors in large participants, compensating filters are recommended. A wedge may also be used as a two-dimensional tissue compensator. If necessary, appropriate reduction in field size must be done to avoid excessive irradiation to critical structures.

12.3.4 Therapy Interruptions

Interruptions in radiotherapy are permissible – and in fact usually indicated – if/when Grade 3 non-hematologic toxicity or Grade 4 hematologic toxicity occurs. Every effort should be made to limit treatment breaks to one week or less.

12.3.5 IMRT

IMRT is discouraged because of potential issues with quality assurance of dosimetry. IMRT is not permitted for tumors that have significant motion with respiration. If IMRT is used, a method for assuring that respiratory motion is being accounted for is mandatory. If you are planning IMRT, contact Dr. Machtay (E-mail: Mitchell.machtay@uhhospitals.org; Phone: 216-844-2530). IMRT will only be approved for centers that have been certified by the RTOG certification process.

12.3.6 Proton Therapy

Proton therapy is discouraged, since it is not currently approved for RTOG therapeutic clinical trials. However, it is recognized that several RTOG member institutions have invested large amounts of scientific resources toward developing programs in proton beam radiotherapy for thoracic malignancies. It is also recognized that the relative biological effect (RBE) of proton beam radiotherapy is similar to that for conventional photon irradiation. Thus, in selected circumstances, selected institutions (subject to Dr. Machtay's approval) may use proton beam radiotherapy if it is deemed in the patient's best interest (for example in order to prevent overdose of normal lung tissue irradiation). Ideally, proton beam radiotherapy should be performed on a (separate) in-house clinical trial rather than ad hoc. Patients treated with proton beam radiotherapy must still be treated with concurrent chemotherapy as well.

If you are planning proton therapy, contact Dr. Machtay (e-mail: mitchell.machtay@uhhospitals.org; phone: 216-844-2530). Centers who use proton therapy

without consent of the PI will have to submit protocol violation paperwork and may face additional consequences.

12.4 Normal Tissue Constraints

12.4.1 Spinal Cord

Maximum spinal cord dose to any point is 48 Gy (including contribution from direct AP-PA beams and scatter from other field arrangements).

12.4.2 Lung

It is strongly suggested that no more than 37% of total lung volume (including both right and left lung but excluding portions of lung involved with tumor/atelectasis/pneumonia) may receive > 20 Gy. This is ideally determined based on formal dose-volume histogram analysis, but may be estimated by physician and physicist using 2-D techniques.

12.4.3 Heart

No specific requirements. Every effort should be made to limit the dose to 50% of the heart to under 40 Gy.

12.4.4 Esophagus

Suggested maximum allowable dose to any point = 66 Gy. It is expected that a large portion of the esophagus will be included in the initial treatment fields. Every effort should be made to limit the amount of esophagus in the conedown fields.

12.5 Reporting of Toxicity (see also Section 13.3)

Since this is a diagnostic study that does not involve any experimental forms of cancer therapy, toxicity reporting will be minimal. ACRIN will collect, record, and report only those adverse events considered possibly, probably, or definitely related during the study participation and up to 30 days after the last study procedure. If a participant is on another prospective treatment trial, adverse event reporting will be based on that treatment trial. Local IRBs and/or institutions may stipulate additional AE reporting based upon their review of the protocol. See Section 16 for more details about adverse events reporting.

13.0 DRUG THERAPY

13.1 Chemotherapy

Participants treated on other prospective treatment trials will be treated as per those trials. Participants treated off protocol will be treated with a combination of a concurrent platin (cisplatin or carboplatin) and a second non-platinum, non-gemcitabine drug (e.g. etoposide, vinblastine, vinorelbine, paclitaxel, or docetaxel). Weekly low dose concurrent chemotherapy may be used (as per RTOG 98-01 or ACR-427), or higher dose intermittent chemotherapy may be used (as per RTOG 94-10). This corresponds to the standard of care for this participant population and is not considered a research or experimental issue for this study.

For participants treated on other prospective treatment trials, information on chemotherapy agents and doses must be submitted to that cooperative group's. Post-XRT adjuvant platinum-based chemotherapy (non-gemcitabine) may be given up until 16 weeks after the completion of XRT. There is no standard post-XRT adjuvant chemotherapy regimen and it is up to the individual institution/physicians. It is recommended that adjuvant gemcitabine be avoided because of its

potentially higher risk of 'radiation recall' pneumonitis, particularly if large radiation fields were used.

13.2 Other Drug Therapy

Prophylactic colony-stimulating factors are not recommended. Prophylactic antibiotics (e.g., trimethoprim/sulfamethoxazole or ciprofloxacin) may be considered as an alternative if there is an expectation that the participants will be significantly immunosuppressed/lymphopenic due to antecedent extremely intensive concurrent chemoradiation and/or steroids.

13.3 Reporting of Chemotherapy/Drug Toxicity (see also Section 12.5)

Since this is a diagnostic study that does not involve any experimental forms of cancer therapy, toxicity reporting will be minimal. ACRIN will collect, record, and report only those adverse events considered possibly, probably, or definitely related during the study participation and up to 30 days after the last study procedure. If a participant is on another prospective treatment trial, adverse event reporting will be based on that treatment trial. Local IRBs and/or institutions may stipulate additional AE reporting based upon their review of the protocol. See Section 16.0 for more details about adverse events reporting.

14.0 PATHOLOGY/TRANSLATIONAL RESEARCH

This section provides information about the RTOG Biospecimen Resource (for participants who have consented to participate in the tissue component of the study).

- 14.1** Participants entered on the main study should be encouraged to provide informed consent to submit materials to the RTOG Biospecimen Resource (see Appendix I for a sample consent form).
- 14.2** The following are to be provided (after the participant has given consent):
 - 14.2.1** One H&E stained slide.
 - 14.2.2** A paraffin-embedded tissue block (or cell block) of the tumor and/or 5 unstained slides (if the quantity of tissue is insufficient for 15 unstained slides, please submit as many as possible). Block/slides must be clearly labeled with identifying information that agrees with the pathology report.
 - 14.2.3** Pathology/cytology report documenting that submitted block or slides contain tumor. Participant's name should be removed from the report. Identify the pathology report with the study number/participant case number in order to protect participant confidentiality.
 - 14.2.4** A Pathology Submission Form must be included and must clearly state that it is being submitted for the RTOG Biospecimen Resource.
- 14.3** RTOG will reimburse pathologists from submitting institutions \$100 per set of slides and \$200 per tissue block. (Note that separate invoice is no longer required.)
- 14.4** The study-specific participant consent form for the pathology/TRP sub-study (included in Appendix I) should give the Pathology Department authority and responsibility to comply with this request (since pathology blocks belong to the participant from whom tissue has been removed).
- 14.5** Submit materials for Tissue Banking, Central Review, or Translational Research as follows:

Mailing Address: For Non-frozen Specimens Only

RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, DHL, etc.): For Frozen Specimens

RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

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

- 14.6** Semi-quantitative immunohistochemical assays for oncoprotein expression and their correlation with PET SUV data and clinical outcome will be performed at University of California, San Francisco. The amount of tissue expected to be collected for this patient population (unresectable NSCLC) is expected to be small, since most patients only undergo a very limited core biopsy, bronchoscopic biopsy or fine needle aspiration. Every attempt will be made to utilize this tissue for the primary translational endpoint (Ki-67 immunohistochemical staining). If there is tissue remaining after this analysis, it may be kept in the tissue bank for future studies on molecular tissue markers of malignancy/cancer unless the participant withdraws consent. There are no plans to perform research related to diseases other than cancer.

15.0 STATISTICAL CONSIDERATIONS

**This section has been
intentionally left blank.**

**This section has been
intentionally left blank.**

**This section has been
intentionally left blank.**

**This section has been
intentionally left blank.**

This section has been intentionally left blank.

16.0 ADVERSE EVENT REPORTING

16.1 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 adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or physiological observations), 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 adverse event.

Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- Results in study withdrawal
- Is associated with a serious adverse event
- Is associated with clinical signs or symptoms
- Leads to additional treatment or further diagnostic tests
- Is considered by the investigator to be of clinical significance

16.2 Definition of Serious Adverse Effect

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence/AE that:

- Results in death;
- Is 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);
- Requires inpatient hospitalization and/or prolongation of an existing hospitalization (hospitalization refers to an overnight admission). 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);
 - Results in a congenital anomaly or birth defect; or
 - Is considered a 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.

If there is any doubt whether the adverse event constitutes a serious adverse event, it should be treated as serious and reported to the ACRIN SAE dedicated phone line at 215-717-2763.

16.3 Adverse Event Grading

Grade refers to the severity (intensity) of the adverse event based on CTCAEv3.0 descriptions.

- 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/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**

16.4 Adverse Event Attribution

Attribution is the determination of whether an adverse event is related to a study treatment or procedure. An adverse event may be considered **associated** with the study treatment or procedure if there is a reasonable possibility that the adverse event was caused by the FDG-PET scan. An adverse event may be considered **NOT associated** with the study treatment/procedure if there is not a reasonable possibility that the adverse event was caused by the FDG-PET scan.

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.

16.5 Reporting of Radiation Therapy Toxicity and Chemotherapy/Drug Toxicity

Since this is a diagnostic study that does not involve any experimental forms of cancer therapy, adverse event reporting will be minimal. ACRIN will collect, record, and report only those adverse events considered possibly, probably, or definitely related to the FDG-PET scan, or any death from any cause that occurs during the study participation and up to 30 days after the post-treatment FDG-PET scan. If a participant is on another prospective treatment trial, adverse event reporting will be based on that treatment trial.

16.6 Expected Adverse Events from FDG-PET Scans

Injection of FDG:

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

PET Scan:

- Discomfort, or
- Claustrophobia

16.7 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 adverse events through discussion and, as appropriate, by examination. Information on all expected and unexpected adverse events considered possibly, probably, or definitely related to the FDG-PET scan with the severity level of grades 1, 2, 3, 4, 5 should be recorded immediately into the source document, e.g. adverse event log and/or progress notes of the study participant's chart, and retained at the site. These adverse events will also be recorded in the AE CRF and reviewed by the principal site investigator in real time to determine grade and attribution of the event.

A **pre-existing condition** is one that is present at the start of the study. A pre-existing medical condition is defined as an adverse event if the frequency, intensity, or character of the medical condition worsens during the study period. At screening visit, any clinically significant findings/abnormalities should be recorded as a pre-existing condition. At the end of study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be documented as adverse events.

16.8 Reporting of Adverse Events

Prompt reporting of all adverse events is the responsibility of each investigator, clinical research associate, and nurse engaged in clinical research. Anyone uncertain about whether a particular adverse event should be reported should contact the ACRIN headquarters at (215) 574-3150 and ask for the ACRIN AE Coordinator for assistance. However, an adverse event report should be submitted if there is a reasonable suspicion of the imaging procedure.

Routine reporting is defined as documentation of adverse events on source documents and AE CRF, and submission to ACRIN 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 National Cancer Institute's Cancer Imaging Program (NCI/CIP) via TRI (Technical Resources International, Inc.) and ACRIN per section 16.8 and 16.9. Routine reporting requirements also apply.

Since this is a diagnostic study that does not involve any experimental forms of cancer therapy, adverse event reporting will be minimal. ACRIN will collect and report only those adverse events considered possibly, probably, or definitely related to the FDG-PET scan with the severity level of grades 1, 2, 3, 4, 5 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 the FDG-PET scan, and serious adverse events identified in section 16.8 will be documented in the study participant's chart and AE case report forms (CRFs), in addition to meeting all study-specific reporting requirements of ACRIN, NCI/CIP, and the local IRB (per local IRB policy).

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse events are otherwise explained. Any death or adverse event occurring at any time after a participant has discontinued or terminated study participation that may be reasonably related to the study imaging effect should be reported.

The following table summarizes the reporting requirements for AEs for the FDG-PET scan:

Adverse Events that occur during study participation (from the first study procedure and up to 30 days after the last study procedure)	Type of Report		
	Routine Reporting	Expedited Written in 10 Working Days	Telephonic Report to NCI/CIP via TRI and ACRIN within 24 hours of knowledge of AE
Grade 1-3 (Attribution of possible, probable, or definite)	X Expected and Unexpected		
Hospitalization/Prolongation of hospitalization** (Attribution of possible, probable, or definite)	X Expected and Unexpected	X Unexpected	
Grade 4 (Attribution of possible, probable, or definite)	X Expected and Unexpected	X Unexpected	
Death (Attribution of possible, probable, or definite)	X Expected and Unexpected	X Expected and Unexpected	X Expected and Unexpected

**All unexpected hospitalizations (or prolongation of existing hospitalization) for adverse events with the severity (intensity) level of CTCAEv3.0 Grade 3, 4, 5 considered possibly, probably, or definitely related to the FDG-PET scan.

Assignment of grades (severity level) and attribution for each AE is to be completed at the site by the Site Principal Investigator.

16.9 Expedited Reporting to NCI/CIP and ACRIN

16.9.1 Investigator or investigator-designee must use expedited adverse event reporting for **all deaths** considered possibly, probably, or definitely related to the FDG-PET scan occurring

during study participation and up to 30 days after the last study procedure. All deaths should be reported by telephone to NCI/CIP via TRI and ACRIN within 24 hours of first knowledge of the event and followed by an expedited written report within ten (10) days. These reports should be sent to ACRIN, NCI/CIP via TRI, and the local IRB, in addition to documentation in patient chart and AE CRF.

- 16.9.2** All life-threatening/disabling unexpected adverse events (considered possibly, probably, or definitely related to the FDG-PET scan) occurring during study participation and up to 30 days after the last study procedure will reported within ten (10) working days of first knowledge of the event. These reports should be sent to ACRIN, NCI/CIP via TRI, and the local IRB, in addition to documentation in patient chart and AE CRF.
- 16.9.3** All hospitalizations (or prolongation of existing hospitalization) for adverse events with the severity (intensity) level of CTCAEv3.0 grade 3, 4, 5 and attribution of possibly, probably, or definitely related to the FDG-PET scan must be reported within ten (10) working days of first knowledge of the event, in addition to documentation in patient chart and AE CRF.
- 16.9.4** All other serious adverse events with attribution of possibly, probably, or definitely related to the FDG-PET scan 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) working 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.
- 16.9.5** Significant new information and/or follow-up information (e.g., test results, autopsy, discharge summary) on on-going serious adverse events should be promptly reported to ACRIN.

16.10 How to Report to the NCI/CIP via TRI and to ACRIN

- 16.10.1** All unexpected fatal adverse events with attribution of possible, probable, or definite and unexpected life-threatening/disabling unexpected adverse events with attribution of possible, probable, or definite should be reported by telephone to NCI/CIP via TRI and ACRIN within 24-hours of the first knowledge of the adverse event.
- 16.10.2** Expedited Telephone Reporting to NCI/CIP via TRI and to ACRIN
 - 16.10.2.1** To make an expedited telephone reports to NCI/CIP, contact TRI staff at (301) 897-1704, available 24 hours a day (recorder after hours from 7:30 PM to 7:30 AM Eastern Time).
 - 16.10.2.2** To make a telephone report to ACRIN, call (215) 717-2763, available 24 hours a day (recorder after hours from 4:30 PM to 8:00 AM Eastern Time).
- 16.10.3** Expedited Written Report Submission to NCI/CIP via TRI and ACRIN
 - 16.10.3.1** An expedited adverse event report requires submission to the NCI/CIP via TRI and ACRIN using the paper templates “Adverse Event Expedited Report—Single Agent” (AdEERS) available on the CTEP home page, <http://ctep.info.nih.gov>.

- 16.10.3.2** Protocols involving only imaging procedures must be submitted using a paper version. (Do not try to send the form via the web site; it will not accept a form without those fields filled in.) Investigators following those protocols should omit the “Course Information” section and the “Protocol Agent” section, even though the template indicates those as mandatory.
- 16.10.3.3** General questions regarding completion of the AdEERS report or submission can be sent to CIPSAEReporting@tech-res.com. The AdEERSMD helpline is available for any questions via phone at (301) 897-7497.
- 16.10.3.4** An expedited adverse event report must be sent with the above-mentioned timeframe to NCI/CIP by fax at (301) 897-7402. All fatal adverse events should be reported by telephone within 24-hours of the event.
- 16.10.3.5** A copy of all expedited adverse event reports should be sent to ACRIN by fax at (215) 940-8819, AND the original (signed and dated) report must be sent to ACRIN headquarters.

**ACRIN 6668 Adverse Event
Attn: ACRIN Adverse Event Coordinator
1818 Market Street, 16th Floor
Philadelphia, PA 19103**

16.11 Adverse Event Reporting and Local IRB

All expedited adverse event reports should be sent to your local IRB per your local IRB policies and procedures. Adverse events not requiring expedited reporting are normally reported to the local IRB in an annual report and/or continuing review report. **Please refer to your local IRB’s policies regarding adverse events/serious adverse events and safety reports.**

17.0 INSTITUTIONAL AUDITS

- 17.1** Initial on-site audits will be completed within 18 to 36 months of a site’s enrolling its first ACRIN participant. Subsequent audits will be scheduled per the outcome of the initial audit. Audits may be required more frequently, but at a minimum every 36 months. Auditors will follow procedures established by the Cancer Imaging Program (CIP) of the NCI. Instructions for preparing for the audit will be sent to sites in advance of the audit date. With these instructions, the auditors will specify which case records will be reviewed during the audit. Auditors will review on-site records against the submitted form, and they will record their findings on specially prepared questionnaires. Major discrepancies will be forwarded to the appropriate oversight body within ACRIN. IRB procedures, approvals, and consent forms will also be reviewed at the audit. The ACRIN Audit Manual is available online at www.acrin.org/pdrc.aspx.
- 17.2** To help sites prepare for audits and assure that clinical RAs maintain records appropriately, the ACRIN data management and auditing departments will offer training. This training will cover all aspects of data collection, but will include special instructions for finding and filing the kinds of source documentation needed to verify the accuracy of submitted data for this trial. **Please refer to the study-specific protocol audit guidelines for details.**

17.3 Source Documents

Source data are found in all information, original records of findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents represent the first recording of any observations made or data generated about a study participant while he or she is enrolled in a clinical trial. Source documents for each study participant substantiate the data that are submitted to ACRIN.

Source documents must verify the eligibility criteria and data submitted on all CRFs. If an item is not mentioned (e.g., history and physical with no mention of a psychological condition), it will be assumed it is not present.

Research records for each case should contain copies of the source documents for the data reported to ACRIN. If data is abstracted from medical charts that are not filed at the investigative sites (e.g. hospital charts), copies of these records should be filed in the research chart. However, every attempt must be made to obtain all records/charts that were used to abstract any study data for this protocol at the time of the audit visit. This will prevent any discrepancies and the inability to verify the document and the data reported.

17.4 Case Report Forms

Case report forms (CRFs) are the primary data collection instruments for the study. All data requested on the CRFs must be recorded, and any missing data must be explained. If a space is left blank because the procedure was not done or the question was not asked, “N/D” must be noted. If the item is not applicable to the individual case “N/A” must be noted. All entries must be printed legibly in black ink on the paper case report forms. In the event of any entry errors, corrections must be made by drawing a **single straight line** through the incorrect entry, writing **the initials of the person making the correction, recording the date** when the correction is being made, and entering the correct data above the strike through. Do not use white out or an eraser.

Data elements that are extracted from the medical record (such as participant history or official clinical interpretations of images, pathology, or surgery results) and recorded on the CRFs will be audited against the appropriate component of the medical record. Data elements gathered from signed participant questionnaires may be documented on the CRF. The image interpretation data required by the study that is a more detailed extraction of information from the image and is not typically documented in the standard radiology report may be recorded on the CRF and is accepted as source documentation **if signed by the Investigator**. At the time of audit, the auditor will verify the occurrence of the imaging examination, the reader, and the date on which the exam took place from the medical record. **Any use of an approved CRF as source documentation requires that the CRF be signed and dated and refer to the source of the information (participant history or official clinical interpretations of images, pathology, surgery results, etc.).**

Any use of CRFs as source documentation when the protocol has designated the source data will be medical record documentation will be considered a deficiency.

17.5 Institutional Review Board

Sites must obtain local IRB initial approval. Prior to subject registration, a copy of the IRB approval letter for the protocol and the informed consent form must be sent to ACRIN, along with

a copy of the IRB approved informed consent form. Investigator will provide a copy(s) of IRB approval letter(s) for any amendment(s), and copy(s) of annual renewal(s).

17.6 Audit Source Documentation Chart

Case Report Form	Data Items	Source Documentation
Eligibility Checklist (Appendix II/ A0)	Confirmed NSCLC Stage IIB or IIIA /IIIB (see section 5.1 & 5.2 of the protocol for the required Inclusion and Exclusion criteria)	Pre-study pathology report, pre-enrollment conventional imaging (CT/MRI) reports, laboratory reports, hospital or clinic chart with documented verification of eligibility and legible copy of AO form signed and dated by the RA
	Zubrod performance status 0-1	
	Absence of stage IV disease	
	Treatment plan	
Initial Evaluation Form (I1)	Confirmed NSCLC Stage IIB or IIIA /IIIB (see section 5.1 & 5.2 of the protocol for the required Inclusion and Exclusion criteria)	Pre-study pathology report, pre-enrollment conventional imaging (CT/MRI) reports, laboratory reports, hospital or clinic chart with documented verification of eligibility and legible copy of I1 form signed and dated by the participant and/or the RA
	Zubrod performance status 0-1	
	Absence of stage IV disease	
	Treatment plan	
Pet Technical Assessment Form (TA)	Pre- and Post-treatment PET imaging reports	Pre- and Post-treatment PET imaging reports and the TA form signed and dated by the local Nuclear Medicine Radiologist
Local Pet Semi- Quantitative Assessment Form (IM)	Pre- and Post-treatment PET imaging reports	Pre- and Post-treatment PET imaging reports and the IM form signed and dated by the local Nuclear Medicine Radiologist
Chemotherapy Summary Form (TF)	Chemotherapy summary of treatment	Chemotherapy flow sheets and/or, hospital/clinic chart chemotherapy treatment documentation and TF form signed and dated by the RA
	Treatment start/end date	
Radiotherapy Summary Form (T1)	XRT start/end date	Radiotherapy treatment record and/or hospital/clinic radiotherapy treatment summary documentation and T1 form signed and dated by the RA and/or Dosimetrist.
	XRT dose summary	
Follow-up Assessment (F1)	Patient status	Hospital and/or clinic chart documentation/ progress notes; Pathology reports, imaging reports, additional treatment summary reports; F1 signed and dated by the RA
	Disease status	
	Interim treatment	
	Continuing or new treatment related events	

Upstaging Form (O1)		Pathology reports, imaging reports, hospital/clinic chart documentation/progress notes, treatment records and O1 signed and dated by a treating Physician
Adverse Event Form (AE)		Medical record documentation of the event and the AE form signed and dated by the Radiologist, RA, or both.
Protocol Variation Form (PR)	Protocol variations	As needed, signed and dated by the PI and the RA

Clinical reports identified as source documentation must include patient's name, date of imaging or procedure, the clinical information, and the signature of the examiner/reader.

All study related documents, including above noted study documentation, will be reviewed and monitored by a monitor, auditor, and/ or quality assurance reviewer.

REFERENCES

1. Cox JD, Azarnia N, Byhardt RW, et al: N2 (clinical) non-small cell carcinoma of the lung: prospective trials of radiation therapy with total doses 60 Gy by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 20:7-12, 1991
2. Durci ML, Komaki R, Oswald MJ, et al: Comparison of surgery and radiation therapy for non-small cell carcinoma of the lung with mediastinal metastasis. *Int J Radiat Oncol Biol Phys* 21:629-636, 1991
3. Komaki R, Cox JD, Hartz AJ, et al: Characteristics of long-term survivors after treatment for inoperable carcinoma of the lung. *Am. J. Clin. Oncol.* 8:362-370, 1985
4. Perez CA, Pajak TF, Rubin P, et al: Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the RTOG. *Cancer* 59:1874, 1987
5. LeChevalier T, Arriagada R, Quoix E, et al: Radiotherapy alone vs. combined chemotherapy and radiotherapy in nonresectable non-small cell lung cancer: first analysis of a randomized trial in 353 patients. *J. National Cancer Inst.* 83:417-23, 1991
6. Dillman RO, Seagren SL, Propert KJ, et al: A randomized trial of induction chemotherapy plus high-dose radiation vs. radiation alone in stage III non-small cell lung cancer. *N. Engl. J. Med.* 323:940-45, 1990
7. Schaake-Konig C, Van dan Bogaert W, Dalesio O, et al: Effects of concomitant cisplatin and radiotherapy on inoperable non-small cell lung cancer. *N. Engl. J. Med.* 326:524-530, 1992
8. Sause WT, Scott C, Taylor S, et al: Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small cell lung cancer. *J. National Cancer Inst.* 87:198-205, 1995
9. Jeremic B, Shibamoto Y, Acimovic L, et al: Hyperfractionated radiation therapy with or without concurrent low-dose daily carboplatin/etoposide for stage III non-small cell lung cancer: a randomized study. *J Clin Oncol* 14:1065-1070, 1996
10. Marino P, Preatoni A, Cantoni A: Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in stages IIIa and IIIb nonsmall cell lung cancer: A meta-analysis. *Cancer* 76:593-601, 1995
11. Stewart LA: The Non-small cell Lung Cancer Collaborative Group: Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ* 311:899-909, 1995
12. ASCO: Clinical practice guidelines for the treatment of unresectable non-small-cell lung cancer. *J Clin Oncol* 15:2996-3018, 1997
13. Saunders M, Dische S, Barrett A, et al: Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. *Radiother Oncol* 52:137-148, 1999
14. Graham MV, Purdy JA, Emami B, et al: 3-D conformal radiotherapy for lung cancer: the Washington University experience. *Front Radiat Ther Oncol* 29:188-198, 1996
15. Armstrong JG, Zelefsky MJ, Leibel SA, et al: Strategy for dose escalation using 3-dimensional conformal radiation therapy for lung cancer. *Ann Oncol* 6:693-697, 1995
16. Rosenzweig KE, Sim SE, Mychalczak B, et al: Elective nodal irradiation in the treatment of non-small cell lung cancer with 3-dimensional conformal radiation therapy. *Int J Radiat Oncol Biol Phys* 50:681-685, 2001
17. Gandara DR, Lovato LC, Albain KS, et al: Prolonged survival in pathologic stage IIIB NSCLC with concurrent chemoradiotherapy followed by consolidation docetaxel: a phase II study (S9504) of the SWOG (abstr. #1916), *Proc. Am. Soc. Clin. Oncol. (ASCO)*. New Orleans, 2000, pp 490a

18. Choy H, DeVore RD, Akerley W, et al: Sequential phase II studies of paclitaxel +/- carboplatin and radiation therapy (+/- hyperfractionation HFXRT) for locally advanced NSCLC: Multi-Institutional trials (abstr. #1951), Proc. Am. Soc. Clin. Oncol. (ASCO). New Orleans, 2000, pp 499a
19. Curran W, Scott C, Langer C, et al: Phase III Comparison of Sequential vs. Concurrent Chemoradiation for Pts. with Unresected Stage III Non-Small Cell Lung Cancer (NSCLC): Initial Report of Radiation Therapy Oncology Group (RTOG) 9410 (abstr.), 9th World Conf on Lung Cancer (IASCLC). Tokyo, 2000
20. Perez CA, Stanley K, Rubin P, et al: A prospective study of various radiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lung: preliminary report by the Radiation Therapy Oncology Group. *Cancer* 45, 1980
21. Perez CA, Stanley K, Grundy G, et al: Impact of irradiation technique and tumor extent in tumor control and survival of patients with unresectable non-oat cell carcinoma of the lung: report by the RTOG. *Cancer* 50:1091-1099, 1982
22. Williams TE, Thomas CRJ, Turrisi ATr: Counterpoint: better radiation treatment of non-small cell lung cancer using new techniques without elective nodal irradiation. *Semin Radiat Oncol* 10:315-323, 2000
23. Robertson JM, TenHaken RK, Hazuka MB, et al: Dose escalation for non-small cell lung cancer using conformal radiation therapy. *Int J Radiat Oncol Biol Phys* 37:1079-1085, 1997
24. Rosenzweig KE, Hanley J, Mah D, et al: The deep inspiration breath-hold technique in the treatment of inoperable non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 48:81-87, 2000
25. Schwegler N, Vrh N, Kern T, et al: Local efficiency of percutaneous radiotherapy in lung cancer. Analysis of 215 repeated bronchoscopies in relation to applied radiation dose (German). *Strahlentherapie und Onkologie* 172:81-90, 1996
26. Robnett TJ, Hahn SM, Shrager JB, et al: Pathologic response to preoperative chemoradiation worsens with anemia in non-small cell lung cancer (NSCLC) patients. Abstr #256, Proc. Radiological Society of North America (RSNA). Chicago, 2000
27. Byhardt RW, Scott C, Sause WT, et al: Response, toxicity, failure patterns, and survival in five Radiation Therapy Oncology Group (RTOG) trials of sequential and/or concurrent chemotherapy and radiotherapy for locally advanced non-small cell carcinoma of the lung. *Int J Radiat Oncol Biol Phys* 42:469-478, 1998
28. Curran WJ, Scott C, Langer C, et al: Phase III comparison of sequential vs. concurrent chemoradiation for pts with unresected stage III NSCLC: Initial report of RTOG 9410 (abstr. #1891), Proc. Am. Soc. Clin. Oncol. (ASCO). New Orleans, 2000, pp 484a
29. Furuse K, Fukuoka M, Kawahara M: Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small cell lung cancer. *J Clin Oncol* 17:2692-2699, 1999
30. Dales RE, Stark RM, Raman S: Computed tomography to stage lung cancers: approaching a controversy using meta-analysis. *Am Rev Respir Dis* 141:1096-1101, 1990
31. Webb WR, Gastsonis C, Zerhouni EA, et al: CT and MR imaging in staging non-small cell bronchogenic carcinoma: report of the radiologic diagnostic oncology group. *Radiology* 178:705-713, 1991
32. Dwamena BA, Sonnad SS, Angobaldo JO, et al: Metastases from non-small cell lung cancer: mediastinal staging in the 1990's -- meta-analytic comparison of PET and CT. *Radiology* 213:530-536, 1999
33. Marom EM, McAdams HP, Erasmus JJ, et al: Staging non-small cell lung cancer with whole-body PET. *Radiology* 212:803-809, 1999
34. Dunagan D, Chin RJ, McCain T, et al: Staging by positron emission tomography predicts survival in patients with non-small cell lung cancer. *Chest* 119, 2001

35. Pieterman RM, van Putten JWG, Meuzelaar JJ, et al: Preoperative Staging of Non-Small-Cell Lung Cancer with Positron-Emission Tomography. *N Engl J Med* 343:254-261, 2000
36. vanTinteren H, Hoekstra OS, Smit EF, et al: Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. *Lancet* 359:1388-1393, 2002
37. MacManus MP, Hicks RJ, Wada M, et al: Early F-18 FDG-PET response to chemoradiotherapy correlates strongly with survival in unresectable non-small cell lung cancer (abstr #1888), *Proc Am Soc Clin Oncol (ASCO)*. New Orleans: 483a, 2000
38. MacManus MP, Hicks RJ, Salminen E, et al: PET response is the most powerful predictor of survival after radical radiotherapy/chemoradiotherapy for unresectable non-small cell lung cancer (abstr. #158), *Proc. Am. Soc. Ther. Radiol. Oncol (ASTRO)*, *Int J Radiat Oncol Biol Phys*: 89, 2001
39. MacManus MP, Wong K, Hicks RJ, et al: Early mortality after radical radiotherapy for NSCLC: comparison of PET-staged and conventionally staged cohorts treated at a large tertiary referral center. *Int J Radiat Oncol Biol Phys* 52:351-361, 2002
40. MacManus MP, Hicks R.J, Ball DL, et al: F-18 fluorodeoxyglucose positron emission tomography staging in radical radiotherapy candidates with nonsmall cell lung carcinoma: powerful correlation with survival and high impact on treatment. *Cancer* 92:886-895, 2001
41. Vansteenkiste JF, Stroobants SG, Dupont PJ, et al: Prognostic importance of the standardized uptake value on F-18 FDG-PET scan in non-small cell lung cancer: an analysis of 125 cases. *J Clin Oncol* 17:3201-3206, 1999
42. Abe Y, Matsuzawa T, Fuziwara T, et al: Clinical assessment of therapeutic effects on cancer using F-18 FDG and PET -- preliminary study of lung cancer. *Int J Radiat Oncol Biol Phys* 19:1005-1010, 1990
43. Hebert ME, Lowe VJ, Hoffman JM, et al: Positron emission tomography in the pretreatment evaluation and followup of non-small cell lung cancer patients treated with radiotherapy: preliminary findings. *Am J Clin Oncol* 19:416-421, 1996
44. Rosenzweig KE, Erdi Y, Schoder H, et al: Positron emission tomography after three-dimensional conformal radiation therapy for non-small cell lung carcinoma (abstr. #159), *Proc. Am. Soc. Ther. Radiol. Oncol. (ASTRO)*, *Int J Radiat Oncol Biol Phys*, 2001, pp 89
45. Bury T, Corhay JL, Duysinx B, et al: Value of FDG-PET in detecting residual or recurrent nonsmall cell lung cancer. *Eur Respir J* 14:1376-1380, 1999
46. Tomlinson S, Russo SM, Bourland JD: Radiation treatment planning with positron emission tomography (PET) imaging for lung cancer alters computed tomography (CT) defined tumor and treatment volumes (abstr. #2228), *Proc. Am. Soc. Ther. Radiol. Oncol. (ASTRO)*, *Int J Radiat Oncol Biol Phys*: 343, 2001
47. Nestle U, Walter K, Schmidt S, et al: 18F-deoxyglucose positron emission tomography (FDG-PET) for the planning of radiotherapy in lung cancer: high impact in patients with atelectasis. *Int J Radiat Oncol Biol Phys* 44:593-597, 1999
48. Mah K, Caldwell CB, Ung YC, et al: The impact of (18) FDG-PET on target and critical organs in CT-based treatment planning of patients with poorly defined non-small-cell lung carcinoma: a prospective study. *Int J Radiat Oncol Biol Phys* 52:339-350, 2002
49. Erdi YE, Rosenzweig K, Erdi AK, et al: Radiotherapy treatment planning for patients with non-small cell lung cancer using positron emission tomography (PET). *Radiother Oncol* 62:51-60, 2002
50. Caldwell CB, Mah K, Ung YC, et al: Observer variation in contouring gross tumor volume in patients with poorly defined non-small cell lung tumors on CT: the impact of FDG-hybrid PET fusion. *Int J Radiat Oncol Biol Phys* 51:923-931, 2001
51. Pauwels EKJ, Sturm EJC, Bombardieri E, et al: Positron-emission tomography with F-18 FDG Part I: biochemical uptake mechanism and its implication for clinical studies. *J Cancer Res Clin Oncol* 126:549-559, 2000

52. Higashi K, Ueda Y, Ayabe K, et al: FDG PET in the evaluation of the aggressiveness of pulmonary adenocarcinoma: correlation with histopathological features. *Nucl Med Commun* 21:707-714, 2000
53. Vesselle H, Schmidt RA, Pugsley JM, et al: Lung cancer proliferation correlates with F-18 FDG uptake by positron emission tomography (PET). *Clin Cancer Res* 6:3837-3844, 2000
54. Lin, LI. A concordance correlation coefficient to evaluate reproducibility. *Biometrics* 45:255-268,1989
55. King et. Al. A Generalized Concordance Coefficient for Continuous and Categorical Data. *Statistics in Medicine* 20:2131-2147, 2001
56. Lachin JM. Introduction to sample size determination and power analysis for clinical trials. *Controlled Clinical Trials* 2:93-113,1981
57. Reed CE, Harpole DH, Posther KE, et al. Results of the American College of Surgeons Oncology Group (ACOSOG) Z0050 Trial: The utility of PET in staging patients with potentially operable non-small cell lung cancer. *J Thorac Cardiovasc Surg*, in press
58. Mac Manus MP, Hicks RJ, Matthews JP, McKenzie A, Rischin D, Salminen EK, Ball DL. Positron emission tomography is superior to computed tomography scanning for response-assessment after radical radiotherapy or chemoradiotherapy in patients with non-small-cell lung cancer. *J Clin Oncol*. 2003 Apr 1; 21(7): 1285-92

APPENDIX I: SAMPLE INFORMED CONSENT FORM

ACRIN #6668/RTOG 0235

Positron Emission Tomography Pre- and Post-treatment Assessment for Locally Advanced Non-small Cell Lung Carcinoma

ACRIN (Nuclear medicine/radiologist) Investigator & phone number:

RTOG (Radiation oncologist) Investigator & phone number:

You are being asked to take part in a clinical study involving PET scans and lung cancer. Clinical trials include only participants who choose to take part. Please take your time to make your decision. You may discuss it with your friends and family. The National Cancer Institute (NCI) booklet *Taking Part in Clinical Trials: What Cancer Patients Need To Know* is available from your doctor. You can learn more about clinical trials at <http://cancertrials.nci.nih.gov>. That web site also has information about PET scans.

You are being asked to take part in this study because you have locally advanced lung cancer.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to determine if a special type of medical body scan (imaging pictures of the inside of the body) can help doctors decide if radiation and chemotherapy are working against your cancer. This type of scan is called a positron emission tomography (PET) scan.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 250 people will take part in this study across the U.S. and Canada.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

If you take part in this study you will have the following tests and procedures.

Standard medical procedures that are part of regular cancer care and would probably be done even if you do not join the study:

- Physical exam before treatment and every 1-2 weeks during treatment
- Blood tests before treatment and every 1-2 weeks during treatment
- Computed tomography (CAT) scan of your chest before treatment
- CAT scan or magnetic resonance (MRI) scan of your head before treatment
- Bone scan before treatment
- Radiation therapy – daily treatments with radiation aimed at your lung/chest
- Chemotherapy (cancer fighting drugs) through a vein in your arm
- Pregnancy test (if applicable)

Standard medical procedures that are being done specifically because you are in this study (These may or may not be done if you were not in this study):

Before starting chemotherapy and radiation, you will have a positron-emission tomography (PET) scan. Do not eat or drink for 4 hours before the PET scan. Before the PET scan you will have a blood sample taken (from a finger-stick or from a vein in the arm). Then, you will be given an injection of a small amount of a radioactive tracer (a chemical similar to sugar which is called FDG) into a vein in your arm or hand.

Approximately 45 minutes after the injection of FDG, you will be asked to go to the bathroom (urinate) and then lie on a partially enclosed scanning table. This procedure is similar to a CT scan. You will need to lie still for about 20-60 minutes before coming off of the scanning table. Your doctors may ask you to go back onto the scanning table for some additional pictures after the initial set is obtained.

The entire PET scan procedure is expected to take about 2 hours.

Once you have had your PET scan, you will receive both radiation therapy to your chest and chemotherapy. The radiation therapy and chemotherapy are not part of this study but are part of standard care. You and your doctor will decide how many radiation and chemotherapy treatments you will get. You will see your doctor at least once a week during radiation therapy. Towards the end of radiation therapy, you may need to see your doctor more often.

About 3 months after your radiation treatments are finished, you will have another PET scan as part of this study. This will be done exactly the same way as described above. Three or four months after you finish radiation and chemotherapy you will have another CAT scan of your chest.

You will continue to see your doctor once the radiation treatments have ended. You will see your doctor every 3 months for the first two years, then every 6 months for another one to three years. Information gathered by your doctor as part of your normal follow-up visits will be given to the study doctors so they can find out more about your health. If you are participating in another study administered by the Radiation Therapy Oncology Group (RTOG), your follow-up care will be given based on that study's protocol. If you are not on an RTOG study, your follow-up care will be given based on your doctor's recommendations.

HOW LONG WILL I BE IN THE STUDY?

We expect that you will be in active treatment for about seven months. You will then need to see your doctor(s) for follow-up visits for the next three years.

This schedule of follow-up visits is the same as that recommended by most cancer doctors for patients who are not part of a clinical study.

You can stop participating in this study at any time. However, if you decide to stop participating, we encourage you to talk to the study doctor and your regular doctor(s) first.

The study doctor may decide to take you off this study if your cancer gets worse or if the side effects of the cancer treatment are very serious. The study doctor may also take you off if new information becomes available that suggests that this treatment will not work or will be

unsafe for you. It is unlikely, but the study may be stopped early due to lack of funding or participation.

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after the PET scan. In some cases, side effects can be serious, long lasting or may never go away.

Risks Associated with PET Scans: This research study involves exposure to radiation from an injection of a radioactive sugar (FDG) for the PET scans. The radiation exposure you will receive from this procedure is equal to a uniform whole-body exposure of approximately 1.5 rem (a measure of radiation exposure) for each PET scan. This is about 60% of the allowable annual dose for radiation workers (for example, x-ray technicians). The risk from this level of radiation exposure is too small to be measured and is small when compared with other everyday risks. If you would like more information about radiation exposure, please speak with your doctor.

Less Likely

Discomfort from lying still on the enclosed scanning table
Bruising or bleeding at the site of injection of FDG
Infection at the site of injection of FDG

Rare But Serious

An allergic-type or other adverse reaction to the radioactive drug (FDG)

Reproductive Risks:

Because PET scans can damage an unborn baby, you should not become pregnant or father a baby while on this study. (The risks of fetal injury, however, are far greater from the radiation and chemotherapy that will be used to treat your cancer.) You should not nurse your baby while on this study. It is important you understand that you need to use birth control while on this study. Ask your study doctor about what kind of birth control methods to use and how long to use them. If you are a woman who can become pregnant you must agree to a pregnancy test (blood test) before each PET scan, before starting treatment (radiation/chemotherapy), and later on if your physician considers it necessary.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, your doctor(s) may learn more information from the PET scans about the location, activity, and other characteristics of your cancer, but this may or may not be of direct medical benefit to you. The main benefits of this study, however, are not to you but to future people with lung cancer.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

You may choose to not participate in this study. You could have PET scans done without participating in this study.

Please talk to your regular doctor about this and other options.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Records of your progress and any images submitted (such as PET scan or CT scan) while you are on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN) and the Radiation Therapy Oncology Group (RTOG) in Philadelphia. Your personal information may be given out if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (FDA), the American College of Radiology (ACR), researchers at the Medical Center of the University of Pennsylvania, and the National Cancer Institute (NCI) and its authorized representatives.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

Taking part in this study may lead to added costs to you or your insurance company. PET scans for lung cancer are usually covered by most insurance companies, but this is not guaranteed. Please ask your doctor(s) about any expected added costs or insurance problems.

You will not be paid for taking part in this study.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, (name), if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at (telephone number).

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor, (name), at (telephone number).

For questions about your rights while taking part in this study call the (name of center) Institutional Review Board (a group of people who review the research to protect your rights at (telephone number).

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be part of the main study even if you say “no” to taking part in any of these additional studies.

CONSENT FORM FOR USE OF TISSUE FOR RESEARCH

About Using Tissue for Research

You have had a biopsy (removal of a small piece of your body tissue) that proved that you have lung cancer. The tissue that was removed for this biopsy was used to do some tests. The results of these tests were given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for research. If you agree, this tissue will be kept at a central storage facility under the direction of the University of California, San Francisco. The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over tissue for future research is up to you. No matter what you decide to do, it will not affect your care. You may still participate in the clinical trial “ACRIN 6668/RTOG 0235, Positron Emission Tomography Pre- and Post-treatment Assessment for Locally Advanced Non-small Cell Lung Carcinoma” even if you do not agree to participate in the tissue research portion of this study.

If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then we will ensure that your tissue is destroyed or will ensure that all information that could identify you is removed from the tissue. You may also request that your tissue be returned to you or your designee.

In the future, people who do research may need to know more about your health. While the American College of Radiology Imaging Network (ACRIN) may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future. If this occurs, you will not be paid.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

The benefits of research using tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THIS STUDY?

The greatest risk to you is the release of information from your health records. The tissue-sample information provided to the University of California, San Francisco should be de-identified (that is, your name, address, phone number and other personal identifying information should be removed) to protect your privacy. The chance that this information will be given to someone else is very small.

APPENDIX II: ELIGIBILITY CHECK & REGISTRATION QUESTIONS

ELIGIBILITY CHECK

(A response coded other than prompted renders a patient ineligible for enrollment)

ACRIN Institution # _____

ACRIN 6668

Case # _____

- _____ (Y) 1. Is there pathologically proven non-small cell lung carcinoma?
- _____ (N) 2. Does the patient have diffuse bronchoalveolar carcinoma?
- _____ (Y) 3. Is the clinical stage IIB or III?
- _____ (Y) 4. Is the Zubrod performance status 0 or 1?
- _____ (N) 5. Has the patient had a head CT or MRI showing evidence of brain metastases?
- _____ (Y) 6. Age \geq 18?
- _____ (Y) 7. Is the patient medically able to tolerate and be compliant with full body PET scans before and after treatment?
- _____ (N) 8. Does the patient have poorly controlled diabetes, defined as fasting blood glucose > 200 mg/dl?
- _____ (N) 9. Is definitive surgery planned as part of the patient's treatment?
- _____ (N) 10. Has the patient had prior thoracic radiotherapy?
- _____ (Y) 11. Is the patient going to be treated with definitive, concurrent chemoradiotherapy at an RTOG member institution?
- _____ (N) 12. Is the treatment plan anticipated to include adjuvant chemotherapy that extends beyond 16 weeks after the completion of radiotherapy?
- _____ (Y/N) 13. Has the patient had a prior cancer other than basal or squamous skin cancer or carcinoma in situ?
- _____ (Y) 13a. If yes, has the patient been disease free for at least 3 years?
- _____ (Y/NA) 14. Has a pregnancy test been done and shown to be negative within 7 days of registration?

_____ (Y/NA) 15. If of reproductive potential, has the patient agreed to use medically acceptable form of contraception throughout the study period and at least 3 months after the second (post-treatment) PET scan?

_____ (Y) 16. Has the patient signed an IRB-approved study specific consent form?

ACRIN Institution # _____

ACRIN 6668

REGISTRATION QUESTIONS

Case # _____

The following questions will be asked at Study Registration:

- _____ 1. Name of institutional person registering this case
- _____ (Y) 2. Has the Eligibility Checklist (above) been completed?
- _____ (Y) 3. Is the patient eligible for this study?
- _____/_____/_____
(mm / dd / yyyy) 4. Date the study-specific Consent Form was signed? (must be prior to study entry)
- _____ 5. Participant's Initials (Last, First) (L, F)
- _____ 6. Verifying Physician (ACRIN M.D.)
- _____ 7. Verifying Physician (RTOG M.D.)
- _____ 8. RTOG institution number
- _____/_____/_____
(mm / dd / yyyy) 9. Date of Birth
- _____ 10. Ethnic Category
- 1 Hispanic or Latino
 - 2 Not Hispanic or Latino
 - 9 Unknown
11. Race (check all that apply)
- American Indian or Alaskan Native
 - Asian
 - Black or African American (not Latino)
 - Native Hawaiian or other Pacific Islander
 - White
 - Unknown
- _____ 12. Gender
- 1 male
 - 2 female
- _____ 13. Participant's Country of Residence (if country of residence is other, complete Q14)
- 1 United States
 - 2 Canada
 - 3 Other
 - 9 Unknown
- _____ 14. Other country, specify (completed only if Q13 is coded **other**)

- _____ 15. Zip Code
- _____ 16. Participant's Insurance Status
- 1 Private insurance
 - 2 Medicare
 - 3 Medicare and Private insurance
 - 4 Medicaid
 - 5 Medicaid and Medicare
 - 6 Military or Veteran Administration
 - 7 Self-pay
 - 8 No means of payment
 - 9 Unknown/declined to answer
 - 0 Other
- _____ 17. Will any component of the participant's care be given at a military or VA facility?
- 1 No
 - 2 Yes
 - 9 Unknown
- _____/_____/_____
(mm / dd / yyyy) 18. (Calendar base date)
- _____/_____/_____
(mm / dd / yyyy) 19. Registration Date
- _____ 20. Did the participant already have a PET scan (If yes, must be within 6 weeks prior to registration)?
- 1 no
 - 2 yes
- _____ 21. Is the participant going to be treated on another protocol (e.g. RTOG study)?
- 1 no
 - 2 yes
- _____ 21a. If yes, indicate which study.
- _____ 22. Did the participant consent to tissue analysis for the primary translational endpoint of the study?
- 1 no
 - 2 yes
- _____ 23. Did the participant consent to tissue storage and analysis for future translational studies related to cancer?
- 1 no
 - 2 yes
- _____ 24. Did the participant consent to tissue storage and analysis for future translational studies related to non-cancer diseases?
- 1 no
 - 2 yes
- _____ 25. Did the participant consent to allowing to be contacted for future studies?
- 1 no
 - 2 yes
- _____ 26. Date of planned or completed PRE-treatment PET scan

Completed by _____

Date completed _____ / _____ / _____
(mm / dd / yyyy)

Signature of person entering data onto the web

APPENDIX III
ACRIN CREDENTIALING PROCEDURES FOR PET IMAGING

Details of the ACRIN Credentialing Procedures for PET Imaging are available on the ACRIN web site at (www.acrin.org/6668_protocol.aspx). For more detailed information, contact Anthony Levering at alevering@phila.acr.org.

APPENDIX IV
PET IMAGING QUALITY CONTROL STANDARDS
(Detailed criteria/specifications for performance of PET scanning in the study)

Details of the PET Imaging Quality Control Standards are available on the ACRIN web site at (www.acrin.org/6668_protocol.aspx). For more detailed information, contact Anthony Levering at alevering@phila.acr.org.

APPENDIX V
INSTITUTION PARTICIPATION GUIDELINES

The potential participants for this study are RTOG member sites that also meet ACRIN qualifications for participating in this study. We cannot provide a specific list of institutions, but traditionally about 40% of RTOG's 250 member sites will open a trial. To qualify for ACRIN participation, sites must fill out a protocol-specific application (see Appendix VII for more information).

APPENDIX VI
CT ACQUISITION PARAMETERS

Details of the CT Acquisition Parameters are available on the ACRIN web site at (www.acrin.org/6668_protocol.aspx). For more detailed information, contact Anthony Levering at alevering@phila.acr.org.

APPENDIX VII
ACRIN 6668 PROTOCOL-SPECIFIC APPLICATION INFORMATION

Application Process

All participating institutions must be ACRIN-approved institutions and current RTOG members prior to study participation and accrual. The approval process for ACRIN 6668 includes submitting an ACRIN Protocol Specific Application (PSA) and having the PET scanner credentialed for study imaging. Detailed information is available on the ACRIN website (www.acrin.org) under list of current protocols (ACRIN 6668). The complete Protocol-Specific Application is on the ACRIN web site at www.acrin.org/6668_protocol.aspx.