RADIATION THERAPY ONCOLOGY GROUP

RTOG 0515

A COMPARATIVE STUDY OF GROSS TUMOR VOLUME DEFINITION WITH OR WITHOUT PET FUSION FOR PATIENTS WITH NON-SMALL CELL LUNG CARCINOMA

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INDEX

1.0 Introduction
2.0 Objectives
3.0 Patient Selection
4.0 Additional Pretreatment Evaluations/Management
5.0 Registration Procedures
6.0 Radiation Therapy/Functional Imaging
7.0 Drug Therapy
8.0 Surgery
9.0 Other Therapy
10.0 Tissue/Specimen Submission
11.0 Patient Assessments
12.0 Data Collection
13.0 Statistical Considerations

References

Appendix I - Sample Consent Form
Appendix II - Performance Status Scoring
Appendix IV - Radiation Oncologist Designation Form
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SCHEMA (8/7/07)

<table>
<thead>
<tr>
<th>STRATIFY</th>
<th>Treatment Component</th>
<th>Research Component</th>
<th>Compare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of neoadjuvant chemotherapy</td>
<td>Treating physician contours PET/CT and generates the treatment plan. This treatment plan is used to treat the patient and is independent of the research component.</td>
<td>Two non-treating radiation oncologists plan treatment: a) 3D-CRT plan for CT-only data set b) 3D-CRT plan for fused PET/CT data set</td>
<td>PET/CT plan with CT-only plan for each patient: 1. Suitability for definitive treatment 2. GTV definition 3. Toxicity profiles (mean lung dose, mean esophagus dose)</td>
</tr>
</tbody>
</table>

It is intended that the patient will be treated using the contoured targets from the PET/CT simulation.

See Section 5.1 for details of pre-registration site credentialing. NOTE: Participating institutions must be credentialed for RTOG S-0132/ACRIN 6665 or RTOG 0235/ACRIN 6668.

See Section 6.1 for details of the treatment and research components of the study.

Patient Population: (See Section 3.0 for Eligibility)
Stage IIA/IIB or Stage IIIA/IIIB non-small cell lung cancer (NSCLC)

Required Sample Size: 48
(Y) 1. Is there histologic or cytologic confirmation of non-small cell lung carcinoma within 16 weeks of registration?

(Y) 2. Is the AJCC (6th edition) tumor stage one of the following: IIA, IIB, IIIA, or IIIB?

(Y) 3. Is patient’s Zubrod performance status a 0, 1, or 2?

(Y) 4. Is patient at least 18 years of age?

(Y) 5. Has staging been confirmed based on required diagnostic evaluations detailed in protocol Section 3.1?

(N/NA) 6. If applicable, is patient pregnant or lactating?

(Y/NA) 7. If applicable, has patient agreed to use a medically acceptable form of contraception during study participation?

(N) 8. Does the patient have malignant pleural effusion?
The following questions will be asked at Study Registration:

1. Name of institutional person registering this case?
2. Has the Eligibility Checklist (above) been completed?
3. Is the patient eligible for this study?
4. Date the study-specific Consent Form was signed? (must be prior to study entry)
5. Patient’s Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]
6. Verifying Physician
7. Patient’s ID Number
8. Date of Birth
9. Race
10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
11. Gender
12. Patient’s Country of Residence
13. Zip Code (U.S. Residents)
14. Patient’s Insurance Status
15. Will any component of the patient’s care be given at a military or VA facility?
16. Treatment Start Date
17. Name of the treating physician
18. Will neoadjuvant chemotherapy be used?

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

Completed by _____________________________ Date ____________________________
1.0 INTRODUCTION

1.1 Overview

The overall goal of the proposed comparative study is to determine if the information obtained by positron emission tomography (PET), with $2^{[18F]}$fluoro-2-deoxy-D-glucose (FDG) will directly alter the tumor targets using three-dimensional (3D) computed tomography (CT)-based treatment-planning. Based on literature supporting the use of FDG-PET for staging to detect locoregional and distant metastasis in patients with non-small cell lung cancer (NSCLC), the hypothesis of this study is that FDG-PET provides a biological target of the locoregional spread of tumor that will alter the conformal radiotherapy treatment plan.

Inoperable NSCLC has cure rates ranging from 5-32% for Stages I and II disease treated with radiotherapy alone and from 5-15% for Stages IIIA and B disease treated with radiotherapy with or without chemotherapy. Sixty-five to 85% of these patients fail locally. The survival of this patient population cannot be improved without decreasing local failure. This project is an effort to apply FDG-PET to improve local tumor control by better target delineation through functional imaging.

To achieve the greatest health relevance, the techniques and concepts developed in this work must be widely available. In the past, the expensive and demanding PET technology was limited to large academic centers. With the success of PET in oncology, the development of integrated PET/CT scanners, and a more favorable reimbursement climate, PET (and PET/CT) availability is rapidly expanding throughout the United States and the developed world. Thus, if this research is successful, the technology to employ FDG-PET into conformal radiotherapy planning can be implemented beyond a few academic institutions.

1.2 Background and Preliminary Investigations

The diagnosis, staging, treatment, and follow-up of lung cancer are a clinical and therapeutic challenge. Recent radiographic and technological advances in imaging have made it possible to noninvasively extract critical information from the cancer patients, which has greatly increased our ability to stage patients and modify clinical therapeutic decisions. These imaging modalities in NSCLC are plain radiography, CT, and the newest technique, PET (or PET/CT). Plain radiographs and CT are the imaging techniques still most widely used currently in staging patients with lung cancer; however, although each provides significant anatomic information regarding the extent of intrathoracic tumor, these techniques have limited accuracy in the detection and diagnosis of lung cancer. Thus, a more accurate method to delineate the extent of spread of tumor progression in NSCLC is essential for both the staging and the subsequent treatment planning processes.

1.2.1 Expected Outcomes

NSCLC is the leading cause of cancer death in both men (32%) and women (25%) worldwide. Treatment is guided by the stage of the disease. Early-stage lung carcinomas are best treated by surgical resection, with cure rates of 70% for Stage I and 50% for Stage II disease at 5 years. However, most patients are not candidates for surgical resection because of the extent of their disease or because of co-morbid conditions that place them at a high risk for complications or death from the procedure. The current standard of care for patients with localized but inoperable NSCLC is either chemoradiotherapy or radiotherapy alone. With current therapy, the prognosis remains poor, with published 5-year survival rates ranging from 5-32% for Stage I and II patients receiving radiation alone and 17% for Stage III patients receiving both chemotherapy and radiation. Despite radiation doses of $\geq 60$ Gy, local failure occurs in up to 85% of these patients.

1.2.2 FDG-PET in NSCLC Staging

When including staging PET with standard tests, FDG-PET has been shown to detect occult extrathoracic metastasis in 11-14% of patients selected for surgical resection. The data are scarce for alterations in radiotherapy. Mac Manus et al. reported that 30% of their prospective, locally advanced NSCLC population became ineligible for curative radiotherapy because of either metastatic disease or intrathoracic disease too extensive for radical radiation. Two-thirds (20% of total) became palliative because of previously undetected distant metastases. Although much more data are needed, one can envision improved survivals for Stages I-III simply by eliminating patients with occult Stage IV disease.

In lung carcinoma, PET has mainly been used for the evaluation of pulmonary nodules and for staging the mediastinum. FDG-PET has consistently been shown to be more accurate than CT in determining nodal status (81-100% vs. 52-85%, respectively). FDG is more sensitive and
specific than CT in detecting metastatic disease in normal-sized lymph nodes and in the
differentiation of enlarged benign nodes from enlarged nodal metastasis.\textsuperscript{14-17} With sensitivity
above 90% and specificity above 80%, FDG-PET is not perfect, but is far better at predicting
pathologic involvement than CT alone.

1.2.3 Radiotherapy Planned with FDG-PET

Radiotherapy Planned with FDG-PET

Several studies have reported the impact of FDG-PET on radiation treatment volumes in
bronchogenic carcinoma (Table 1). A recent review by Bradley et al. described the
contributions of these studies.\textsuperscript{18} In most of these studies, the additional information provided
by PET has been incorporated through side-by-side comparison of CT and PET images or by
digital overlays of separately obtained PET and CT data (image fusion). In a retrospective
study, Nestle et al. reported that incorporation of PET findings would have altered the shape of
the radiation portals in 12 of 34 patients (35\%).\textsuperscript{19} They used a qualitative visual method to
determine target volumes. Kiffer et al. used a method of graphical co-registration of coronal
PET reconstructions overlaid on fluoroscopic simulation films.\textsuperscript{20} They found inadequate
coverage of the tumor delineated on PET in 4 of 15 patients planned with CT alone. They also
reported an improved demarcation of tumors by PET in three additional patients with
atelectasis. Use of the PET images for planning would have altered the radiation therapy
portals in 7 of 15 patients (47%). Vanuytsel et al. reported a theoretical comparison of gross
tumor volume (GTV) defined by CT and by PET + CT.\textsuperscript{21} All patients had the pathologic extent
of nodal disease mapped by cervical mediastinoscopy. The CT-based and PET + CT–based
nodal maps were compared. PET findings altered the theoretical portal volume in 45 of 73
patients (62\%).

Munley et al. performed a retrospective study of patients with lung cancer who had pre-
irradiation SPECT lung perfusion scintigraphy (n=104) and FDG-PET (n=35) in addition to
standard CT of the thorax used to perform radiation therapy treatment planning.\textsuperscript{22} In the 35
patients in whom CT and PET data were used for treatment planning, 12 (34\%) had portions of
the beam aperture enlarged beyond the initial design based on CT alone. For the majority of
these cases, the PET-defined target volume encompassed the CT-defined target volume, so
the treatment planner had confidence that the difference between the target volumes was not
the result of a co-registration error. Beam orientation based on the CT-defined target was
generally not changed by the PET imaging data.

Mac Manus et al. reported a prospective trial in which diagnostic PET studies were used for
radiation treatment planning (RTP).\textsuperscript{9} Among the 102 patients who underwent definitive
irradiation, PET led to a significant increase in the target volume in 22 because of inclusion of
structures previously considered not involved by tumor. In 16 patients, the target volume was
significantly reduced because PET demonstrated areas of lung consolidation or enlarged
lymph nodes with low FDG uptake, which were excluded from the treatment volume. In 3
patients, primary tumors were seen on PET that were not recognized on CT.

A few recent studies have used radiation therapy simulation based on fusion of CT and FDG-
PET. Mah et al. performed RTP via co-registration of FDG and CT images in 30 patients
undergoing definitive radiation therapy for NSCLC.\textsuperscript{23} Patients in this prospective study were
immobilized for radiation therapy simulation and imaged using a coincidence gamma camera.
Treatment was significantly altered in 12 patients (40\%). The treatment intent became palliative
in 7 patients. The target volume was altered to include nodal disease detected by coincidence
imaging in 5 patients. The treatment volumes based on CT were judged to be inadequate by
comparison to those based on combined CT and FDG imaging in 17-29\% of the cases,
depending on the physician contouring the volumes.

Giraud et al. used gamma camera coincidence imaging of FDG fused with the simulation CT
images by use of external fiducial markers.\textsuperscript{24} Significant alterations in treatment were seen for
5 of the 11 patients (45\%), additional nodal disease was detected in 4, and metastatic disease
was detected in 1. Erdi et al. reported on 11 patients with NSCLC studied with a dedicated
PET scanner who underwent sequential CT and PET simulations.\textsuperscript{25} The planning target volume
(PTV) increased in 7 of 11 patients (64\%) to incorporate additional regional nodal disease.
PET also helped to delineate tumor from atelectasis in 2 patients. In summary, these reported
studies suggest a significant alteration in tumor volume coverage in approximately 30-60\% of
patients with NSCLC planned with FDG images (Table 1).
Table 1: Impact of FDG-PET on Radiation Treatment Volumes in NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Method</th>
<th>Impact on RTP* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hebert et al.26</td>
<td>1996</td>
<td>20</td>
<td>Visual</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>Kiffer et al.20</td>
<td>1998</td>
<td>15</td>
<td>Visual</td>
<td>7 (47%)</td>
</tr>
<tr>
<td>Nestle et al.19</td>
<td>1999</td>
<td>34</td>
<td>Visual</td>
<td>12 (35%)</td>
</tr>
<tr>
<td>Munley et al.22</td>
<td>1999</td>
<td>35</td>
<td>Visual</td>
<td>12 (34%)</td>
</tr>
<tr>
<td>Vanuystel et al.21</td>
<td>2000</td>
<td>73</td>
<td>Image fusion</td>
<td>45 (62%)</td>
</tr>
<tr>
<td>Giraud et al.24</td>
<td>2001</td>
<td>12</td>
<td>Image fusion</td>
<td>5 (42%)</td>
</tr>
<tr>
<td>Erdi et al.25</td>
<td>2002</td>
<td>11</td>
<td>Image fusion</td>
<td>9 (82%)</td>
</tr>
<tr>
<td>Bradley et al.27</td>
<td>2003</td>
<td>24</td>
<td>Image fusion</td>
<td>14 (58%)</td>
</tr>
</tbody>
</table>

*RTP—Radiation treatment planning. These numbers represent patients whose radiation target volumes were either substantially expanded to include additional tumor detected by PET or reduced to exclude regions that were not involved on PET.

1.2.4 Preliminary Data

Bradley et al. prospectively evaluated 26 patients with Stages I-III NSCLC referred for definitive radiation therapy or chemoradiation therapy. All patients underwent CT simulation for radiation therapy followed immediately by FDG-PET. Each patient was accompanied to the PET scanner by a trained radiation therapy technologist and positioned using custom immobilization and external lasers. External fiducial markers were used to fuse the two image data sets for RTP. The CT-alone and PET-CT co-registered images for each patient were maintained separately. The target volume contours were delineated by separate radiation oncologists and compared. The FDG-PET findings altered the American Joint Committee on Cancer (AJCC) TNM stage in 8 of 26 patients (31%); 2 patients were diagnosed with metastatic disease based on FDG-PET and received palliative radiation therapy. Of the 24 patients who were planned with three-dimensional conformal radiation therapy (3DCRT), PET significantly altered the radiation therapy volume outlined in 14 (58%). PET helped to distinguish tumor from atelectasis in all 3 patients with atelectasis. Unsuspected nodal disease was detected by PET in 10 patients. One patient had a separate tumor focus detected within the same lobe of the lung. These results are similar to those in other series described above.

2.0 OBJECTIVES

2.1 Primary Objective

To determine the impact of PET/CT fusion for each patient by comparing gross tumor volume (GTV) contours and 3DCRT treatment plans using two separate data sets (PET/CT and CT only); to determine the impact of PET on the following endpoints: GTV (cm³), number of involved nodes, location of involved nodes, and dosimetric measures of normal tissue toxicity (mean lung dose, V20, and mean esophageal dose). Because the use of PET/CT can both increase and decrease these measures, we will compare the absolute value of the differences for each patient.

2.2 Secondary Objective

To determine the rate of elective nodal failures (nodal failures in regions that are not intentionally irradiated to definitive doses [i.e., ipsilateral hilum, mediastinum, or ipsilateral supraclavicular fossa]).

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (3/2/07)

3.1.1 Pathologically (histologically or cytologically) proven diagnosis of NSCLC within 16 weeks of registration;
3.1.2 Stage IIA/IIB or Stage IIIA/B. Patients with local or regional nodal recurrence following surgery are eligible. The following diagnostic workup is required:

3.1.2.1 History/physical examination within 8 weeks prior to registration
3.1.2.2 Chest CT with intravenous contrast agent administration (radiation therapy planning CT is acceptable) within 8 weeks prior to registration. Note: If a separate abdominal CT is not done, the chest CT must include the liver and adrenal glands.
3.1.2.3 Diagnostic FDG-PET within 8 weeks prior to registration. The planning PET study may be used as the diagnostic PET study, provided the study is officially read by a nuclear medicine physician and scored in accordance with Sections 6.2 through 6.7.
3.1.2.4 Cross-sectional imaging of the brain (head CT or MRI) within 8 weeks prior to registration.

3.1.3 Zubrod Performance Status 0, 1, or 2
3.1.4 Age $\geq 18$
3.1.5 Serum pregnancy test (if applicable); women of childbearing potential and male participants must practice adequate contraception.
3.1.6 Patient must sign study-specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility
3.2.1 Malignant pleural effusion.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT
Not applicable to this study.

5.0 REGISTRATION PROCEDURES
5.1 Pre-Registration Requirements
5.1.1 Participating institutions must be credentialed for RTOG S-0132/ACRIN 6665 or RTOG 0235/ACRIN 6668 and must be able to submit DICOM PET images to the Image-Guided Therapy Center. PET must be obtained with 3DCRT immobilization and setup (see Section 6.4 for details).

5.1.2 Each institution must submit and successfully complete a protocol-specific dry-run case of the PET/CT fusion data set PRIOR TO ENROLLING ANY PATIENTS ON PROTOCOL. The plan will be reviewed centrally at the Image Guided Therapy Center (ITC), and suggestions regarding protocol compliance will be forwarded to the participating institution. Each institution must contact the ITC (itc@castor.wustl.edu) and request an FTP account for digital data submission. Detailed credentialing requirements may be found on the ATC website: http://atc.wustl.edu.

5.1.3 Following the approval of the initial PET/CT fusion database, each institution entering a patient on trial must electronically submit two data sets for central review: the planning CT data set (without PET fusion) and the PET/CT data set. Details of the data to be submitted to the ITC may be found in Section 12.1 and on the ATC website: http://atc.wustl.edu. Gross tumor volumes will be contoured on both data sets. See instructions for contouring in Sections 6.4 and 6.6.

5.2 Registration
5.2.1 Dial-in Registration (3/2/07)
Patients can be registered only after eligibility criteria are met. Additionally, before the first patient is registered to this trial, each institution must provide the registrars at RTOG Headquarters with the names of three radiation oncologists. If one of these physicians leaves the institution or can no longer participate, an alternate should be named as a replacement. This replacement investigator must submit his/her own PET/CT contours from an applicable patient (may be a previously submitted case) for review prior to enrolling a new patient. For any given patient, one radiation oncologist will be involved in patient care only. RTOG Headquarters will assign the physicians responsible for CT and PET/CT treatment planning. No changes in the two physicians responsible for the radiation treatment planning are allowed. At patient registration, RTOG Headquarters will request the name of the treating physician for the patient being registered.

Patients are registered prior to any protocol therapy by calling RTOG Headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.
6.0 **RADIATION THERAPY/FUNCTIONAL IMAGING (8/7/07)**

Institutions should follow the steps below for each patient enrolled on study.

**For the treatment component of the study:**
1. The patient is consented and scanned.
2. Fuse the PET/CT from nuclear medicine.
3. The Dosimetrist contours normal structures.
4. Save 2 extra copies of these images for the research portion of the study.
5. The treating physician contours PET/CT and generates the treatment plan. **This treatment plan is used to treat the patient and is independent of the research plans (below).**

**For the research component of the study:**
Option 1: Non-treating radiation oncologist #1 plans treatment with CT.
   Non-treating radiation oncologist #2 plans treatment with fused PET/CT.

Option 2: Non-treating radiation oncologist #2 plans treatment with CT.
   Non-treating radiation oncologist #1 plans treatment with fused PET/CT.

1. Use the same CTV and PTV margins for both of these research plans.
2. Submit the research contours to the ATC.

6.1 **Radiation Therapy**

**Note: Intensity Modulated RT (IMRT) Is Not Allowed**

It is intended that the treated PTV will be derived from the PET/CT generated volumes. Otherwise, the definitive management of patients entered on this trial will be left to the discretion of the treating physician. The prescribed radiation dose is not expected to affect the study objectives (Section 2.1). Definitive radiation therapy doses must be ≥ 60 Gy for the patient to be followed for occurrence of local, regional, and “elective nodal” failures (Section 2.2). Patients may be treated on other RTOG protocols that omit “elective nodal” irradiation. Specifically, patients enrolled on RTOG 0235/ACRIN 6668 are eligible for this protocol.

For radiotherapy planning information, please reference Sections 6.4.2 and 6.6.2.

6.2 **CT Imaging Studies (3/2/07)**

**6.2.1 CT Imaging for Software Fusion with Images from a Separate Dedicated PET Scanner**

Patients will be positioned in an appropriate immobilizer prior to scanning. Patients will be positioned supine with arms overhead. Intravenous contrast will be used for this scan. A CT reference will be marked for localization at the time of the CT, or an isocenter can be predetermined at fluoroscopic simulation. Fiducial markers for image co-registration (six to eight total) will be placed anteriorly (three to four) and posteriorly (three to four) on the patient's thorax or immobilization device. CT images will be obtained with 3-5mm slice thickness through the volume encompassing the tumor plus 5 cm superiorly and inferiorly. Five-mm slice thickness will be sufficient for volumes beyond this volume. A small metal bead or BB is suggested as the preferred fiducial marker for CT. 4D imaging is allowed.

**6.2.2 CT Imaging with an Integrated PET/CT Scanner**

Patients will be positioned in an appropriate immobilizer prior to scanning. Patients will be supine with arms overhead. The isocenter will be selected and marked for localization. CT images will be obtained with slice thickness appropriate for PET/CT scanner or finer thickness if available (4.25 mm or default setting for specific scanner). The simulation CT may be acquired as part of a whole-body PET/CT acquisition if possible. Alternately, a limited acquisition with scan coverage restricted to region required for simulation is acceptable.

6.3 **Functional Imaging: PET**

**6.3.1 PET Equipment**

PET scanners approved for RTOG 0235/ACRIN 6668 or RTOG S-0132/ACRIN 6665 are approved for this protocol. Either a dedicated PET scanner or an integrated PET/CT scanner is permissible for this study. PET scanners with BGO, LSO, or GSO detectors must be used; scanners with NaI detectors are not acceptable for this trial. For dedicated PET, the scanner must be capable of performing both emission and transmission images, in order to allow for attenuation-corrected PET images. The same scanner must be used for both the pre- and post-
treatment scans. A flat tabletop compatible with the PET scanner is required. For questions about permitted PET scanners, contact either of the Nuclear Medicine Co-Chairs: Dr. Siegel (siegelb@mir.wustl.edu) or Dr. Brunetti (brunetti@mail.holyname.org).

6.3.2 Pre-FDG Injection: Participant Preparation
Participants must fast and not consume beverages containing sugar for at least 4 hours before injection of FDG. Participants also should be encouraged to eat high-protein, low-carbohydrate foods on the day before the study (and especially to avoid carbohydrates for the last meal before fasting). Intravenous feedings or fluids containing glucose also must be withheld for at least 4 hours before injection of FDG. Hydration with either noncaloric oral or intravenous fluids is encouraged. Patients should be instructed to avoid strenuous exercise 24 hours prior to the scan to prevent uptake in recovering muscles. Blood glucose will be measured and recorded within 1 hour before injection of FDG and must be \( \leq 200 \) mg/dL. FDG will be synthesized and prepared in accordance with the institution’s standard procedures or obtained from a commercial supplier.

6.3.3 PET Imaging
The administered activity of FDG should be based on the recommendation of the manufacturer of the specific PET scanner being used for the study. 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). After an uptake period of 50-70 minutes, the patient should empty his or her bladder, and then will be positioned on the flattop table in the PET scanner and immobilized in the cradle by the radiotherapy technologists. Patients being imaged on a dedicated PET scanner should have commercially available PET fiducial markers placed on the thorax to facilitate fusion with the simulation CT. Depending on the patient’s ability to tolerate the treatment planning position, whole-body PET (scan range from the skull base to the proximal thighs) or a limited PET acquisition (scan range equivalent to the CT simulation coverage) may be performed with the patient immobilized. For dedicated PET scanners, a series of transmission scans will be performed (to account for tissue attenuation) in addition to emission scans. The duration of acquisition for transmission and emission data (2D or 3D) 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. PET images will be reconstructed with an iterative algorithm (OSEM) followed by a filter appropriate for the specific scanner. For PET/CT scanners, thoracic fiducial skin markers are not required as images will be pre-registered. A CT scan with parameters previously described in Section 6.2.2. will precede PET acquisition, and CT data will be used for attenuation correction of PET images in accordance with the specific manufacturer’s algorithm. The duration of acquisition for emission data (2D or 3D) 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. 4D PET imaging is allowed.

6.3.4 PET Interpretation (3/2/07)
All PET studies must be reviewed by a nuclear medicine physician or a nuclear radiologist from the institution entering the patient on trial. Verification of this review will be based on completion of the IM data form. The use of standard uptake values (SUVs) for determining malignant involvement or for delineating tumor targets is subjective. Therefore, SUV measurements will not be specifically used to determine tumor targets. All PET images will be reviewed for target contouring by the nuclear medicine radiologist and radiation oncologist assigned to PET/CT fusion at the medical facility where the patient is being imaged and treated. It is expected that the nuclear medicine radiologist will be involved in reviewing contours for purposes of radiation treatment planning.

6.4 Tumor Delineation and Radiotherapy Planning for the CT Data Set
For the purposes of this protocol, two sets of contours will be maintained and compared: a CT-only data set and a fused PET/CT data set. Each institution will be required to designate two radiation oncologists for contouring prior to enrollment.

6.4.1 CT-only Data Set (3/2/07)
The CT-only data set must be contoured before the radiation oncologist’s review of the PET or combined PET/CT images. Gross tumor volume contours will be delineated on the CT images. The primary tumor volume and any regional nodes exceeding a diameter of 10 mm will be identified as tumor. Lung window settings will be used to contour the primary lesion, and soft tissue windows are to be used for contouring the lymph nodes. Elective nodal areas will not be contoured as GTV. A volumetric margin of at least 10 mm for patients planned using techniques to account for tumor motion during lung ventilation (i.e., 4DCT) and 15 mm for patients planned using standard CT simulation will be added to the GTV to define the planning target volume (PTV), encompassing both the primary and nodal gross tumor. Other organs that must be contoured include right lung, left lung, esophagus (from cricoid to gastroesophageal junction), spinal cord, heart, and liver.

6.4.2 3DCRT Planning
A single 3DCRT plan using the PTV derived from the volumetric CT scan only will be performed. Heterogeneity corrections will be used for calculating radiation dose. There are two acceptable methods to prescribe radiation dose: 1) The dose can be prescribed to the ICRU reference point defined in ICRU #50. A minimum PTV isodose coverage also will be recorded. 2) The dose can be prescribed to the PTV (i.e., the prescribed dose covers ≥ 95% of the PTV). The minimum PTV isodose coverage will be recorded. Irradiation will not be intentionally administered to nodal regions identified as normal on PET and CT. The prescribed dose will not be defined by this protocol. The only requirement is that the prescribed dose and prescribing methods be identical for both the CT-only and PET/CT data sets. Dose-volume histograms will be generated for each contoured organ (see Section 6.4.1), GTV and PTV contours.

6.5 Image Registration of CT and PET
For imaging obtained on a combined PET/CT unit, the data sets will be pre-registered, and this section is not applicable.

For separately obtained CT and PET images, the FDG-PET images will be co-registered with the volumetric CT scan. Both the CT and PET data sets will be transferred to an imaging workstation for image segmentation and multi-modality fusion. Fusion software may vary from institution to institution. This software consists of a set of tools for drawing and maintaining groups of contours used in segmenting image data. Transfer of the PET data to the radiation treatment planning system may require reformatting the data to DICOM.

6.6 Tumor Delineation and Radiotherapy Planning for the PET/CT Data Set
6.6.1 PET/CT Data Set (3/2/07)
Gross tumor volume contours will be delineated on the PET/CT images. Because of the difficulties with edge detection inherent in contouring PET volumes, all contoured volumes, both primary tumor and involved nodal disease, will be delineated from the CT portion of the PET/CT study. The primary tumor volume and any regional nodes positive on PET scan exceeding a diameter of 10 mm based on the CT will be identified as GTV. In addition, any hilar or mediastinal lymph nodes measuring < 10 mm in diameter, but demonstrating FDG uptake on PET scan will be contoured as GTV. The primary tumor and each of the involved lymph nodes will be contoured separately. Elective nodal areas will not be contoured as GTV. Tumor contouring is particularly problematic in the case of lung atelectasis. PET imaging can help clarify the tumor in this situation. In the case of atelectatic lung adjacent to gross primary or nodal tumor, only the areas with increased FDG uptake will be considered as GTV (as determined by the nuclear medicine radiologist and radiation oncologist assigned to PET/CT fusion). A volumetric margin of at least 15 mm will be added to the GTV to define the planning target volume (PTV), encompassing both the primary and nodal gross tumor. Other organs that must be contoured include right lung, left lung, esophagus, spinal cord, heart, and liver.

6.6.2 3DCRT Planning
A single 3DCRT plan will be generated from the contoured PET/CT data set. Heterogeneity corrections will be used for calculating radiation dose. There are two acceptable methods to prescribe the dose: 1) The dose can be prescribed to the ICRU reference point defined in ICRU #50. A minimum PTV isodose coverage also will be recorded. 2) The dose can be prescribed to a volume (i.e., the prescribed dose covers ≥ 95% of the PTV). Irradiation will not be intentionally administered to nodal regions identified as normal on PET and CT. The prescribed dose, beam energies, compensating filters, wedges, etc., will not be specified by the protocol. The only requirement is that these parameters be identical for both the CT-only and
PET/CT data sets for each patient registered to the protocol. Dose-volume histograms will be generated for each contoured organ (see Section 6.6.1), GTV, and PTV contours.

6.7 Data Collection

Measurements from the two contoured data sets will be made on the following endpoints and sent to the RTOG Department of Statistics:

- The GTV of the primary tumor plus the involved lymph nodes;
- The number of involved lymph nodes;
- The location of the involved lymph nodes (by AJCC, 6th ed. defined lymph node stations);
- Measures of normal tissue toxicity (total mean lung dose, V20, and mean esophageal dose).

7.0 DRUG THERAPY

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

The definitive management of patients entered on this trial will be left to the discretion of the treating physician. The prescribed chemotherapy regimen is not expected to affect the study objectives (Section 2.1). Neoadjuvant and/or concurrent chemotherapy is permitted.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

Not applicable to this study.

10.0 TISSUE/SPECIMEN SUBMISSION

Not applicable to this study.

11.0 PATIENT ASSESSMENTS (3/2/07)

11.1 Study Parameters

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Pre-Study Entry</th>
<th>3 Months Post Completion of RT</th>
<th>Follow-Up (see Section 11.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History/physical, Zubrod</td>
<td>X(^a)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Chest CT</td>
<td>X(^a,b)</td>
<td>X</td>
<td>X(^e)</td>
</tr>
<tr>
<td>PET</td>
<td>X(^c)</td>
<td>X(^e)</td>
<td>X(^e)</td>
</tr>
<tr>
<td>Head CT/MRI</td>
<td>X(^c)</td>
<td>X(^e)</td>
<td></td>
</tr>
<tr>
<td>Serum pregnancy test</td>
<td>X(^d)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a) Within 8 weeks prior to registration;
b) With contrast; if a separate abdominal CT scan is not done, the chest CT scan must include liver and adrenal glands;
c) Within 8 weeks prior to registration;
d) If applicable;
e) At discretion of attending physician as clinically necessary

11.2 Recommended Evaluation Following Treatment

11.2.1 At each visit, it is recommended that the treating physician complete an interval history, complete physical examination, and assessment of Zubrod performance status.

11.2.2 It is recommended that a chest CT be performed 3 months following completion of radiation therapy, then every 6 months for 2 years, and yearly thereafter.

11.2.3 It is recommended that the treating physician follow the patient every 3 months for the first year, every 6 months for years 2 and 3, and yearly thereafter.

12.0 DATA COLLECTION

12.1 Data Submission to ITC

12.1.1 Digital Data Submission
Digital data submission may be accomplished using media or the Internet. For network submission: The FTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:

\[\text{itc@castor.wustl.edu}\]

For media submission: Please contact the ITC about acceptable media types and formats. Hardcopies accompanying digital data should be sent by mail or overnight delivery and should be addressed to:

\[\text{Image-Guided Therapy Center (ITC)}\]
\[\text{4511 Forest Park, Suite 200} \]
\[\text{St. Louis, MO 63110} \]
\[\text{314-747-5415} \]
\[\text{FAX 314-747-5423} \]

12.1.2 \textbf{Data Submission to ITC Prior to Treatment of First Patient}

Each institution must submit and successfully complete a protocol-specific dry-run test case of the PET/CT fusion data set prior to enrolling any patients on protocol. The data will be reviewed centrally at the Image-Guided Therapy QA Center (ITC), and suggestions regarding protocol compliance will be forwarded to the participating institution. Please see the ATC website (http://atc.wustl.edu) for detailed information regarding the credentialing process.

12.1.3 \textbf{Data Submission to ITC} (Please see the ATC website [http://atc.wustl.edu] for detailed information)

<table>
<thead>
<tr>
<th>Item</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Image Fusion Information</td>
<td>Within 1 week start of RT</td>
</tr>
<tr>
<td>IM Form</td>
<td></td>
</tr>
<tr>
<td>CT Data, if different from planning CT</td>
<td></td>
</tr>
<tr>
<td>PET/CT Data</td>
<td></td>
</tr>
<tr>
<td>Picture of fused images for three orthogonal cuts(^a)</td>
<td></td>
</tr>
<tr>
<td>Initial Dosimetry Information</td>
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<tr>
<td>Digital Data Submission Information Form (DDSI)(^b)</td>
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<tr>
<td>CT Data(^c)</td>
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<tr>
<td>Structures(^c)</td>
<td></td>
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<tr>
<td>Digital Dose Data and Beam Geometry Data(^c)</td>
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</tr>
<tr>
<td>Digital DVH Data(^c)</td>
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</table>

Final Dosimetry Information

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of Treatment Form (T1)</td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>Radiotherapy Treatment Planning Form (V8)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Can be sent as a JPEG via e-mail or as hardcopy printouts via overnight mail.
\(^c\)For each data set separately; one set for CT-only plan and one set for PET/CT plan.

Please see the ATC website (http://atc.wustl.edu) for detailed information regarding data submission requirements.

12.2 \textbf{Summary of Data Submission to RTOG}

Data should be submitted to:

\[\text{RTOG Headquarters} \]
\[\text{1818 Market Street, Suite 1600} \]
\[\text{Philadelphia, PA 19103} \]

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

13.1 Study Endpoints

13.1.1 Primary Endpoint:
The impact of PET/CT fusion for each patient by comparing GTV contours and 3DCRT treatment plans using two separate data sets (PET/CT and CT only). The impact of PET/CT fusion on treatment plans will be measured by differences in the following measurements: gross tumor volume, number of involved nodes, location of involved nodes, and dosimetric measure of normal tissue toxicity, which includes mean lung dose, V20, and mean esophageal dose. Because the use of PET/CT can both increase and decrease the GTV, we will compare the absolute value of the differences for each patient.

13.1.2 Secondary Endpoint:
Elective nodal failure rate.

13.2 Sample Size (3/2/07)

13.2.1 Stratification
Patients will be stratified before randomization with respect to the use of neoadjuvant chemotherapy (yes vs. no). The treatment allocation scheme described by Zelen[28] will be used because it balances patient factors other than institution. The physicians involved in treatment planning will be randomized to PET/CT planning or CT-only planning.

13.2.2 Sample Size Derivation
This study compares treatment plans using PET/CT fusion and CT only. Gross tumor volume, the number of involved nodes, and dosimetric measures of normal tissue toxicity (mean lung dose, V20, and mean esophageal dose) will be used to test the impact of PET/CT. V20 is the percentage of total lung volume (the volume of both lungs minus the PTV) exceeding 20 Gy. In order to compare the five measurements to test one hypothesis, the Type I error will be adjusted for each comparison to insure the overall significance level is preserved. We set the overall Type I error to be 0.05 and use the Bonferroni multiple comparison adjustment. Therefore, the Type I error for each comparison will be 0.05/5=0.01. To determine sample sizes, standard deviations for each of the five measures were calculated using data from patients treated on RTOG 9311.

In order to detect a clinically meaningful difference of 15 cc in absolute value gross tumor volume with 85% statistical power using a one-sided one-sample paired t-test, 38 patients are required. The estimate of the standard deviation used in this calculation was 26.20. A clinically meaningful difference in number of involved nodes is 1. The required sample size to detect this magnitude of difference with an estimated standard deviation of 0.824 using a one-sided one-sample paired t-test with 85% statistical power at a significance level of 0.01 is 11 patients.

Mean lung dose, V20, and mean esophageal dose of NSCLC patients using CT scans were estimated to be 15 Gy (estimated standard deviation 4.61 Gy), 24% (estimated standard deviation 8.9%), and 22 Gy (estimated standard deviation 12.8 Gy), respectively, from RTOG 9311 data. The required sample sizes to detect a clinically meaningful magnitude of difference
of 20% or 3 Gy in mean lung dose, 4.8% in V20, and a clinically meaningful magnitude of difference of 30% or 6.6 Gy in mean esophageal dose using a one-sided one-sample paired t-test with 85% statistical power at a significance level of 0.01, are 30, 42, and 45 patients, respectively. A sample size of 45 patients assures at least 85% statistical power to detect the clinically meaningful difference for each of the five measurements.

Assuming a 5% rate of ineligibility and/or inevaluability, the total sample size required will be 48 patients.

13.2.2 Patient Accrual

The recent RTOG Phase II NSCLC study (0324) accrued an average of 4 patients per month. Based upon this accrual rate, and allowing 6 months for institutional IRB review and approval, accrual should be completed in approximately 18 months. If the average monthly accrual is less than 2 cases per month, the study will be re-evaluated with respect to feasibility.

13.3 Analysis Plan

13.3.1 Interim Reporting of Accrual

Interim reports will be prepared every 6 months until the primary endpoint has been presented. In general, these reports include:

- the patient accrual rate with projected completion date
- institutional accrual
- the distribution of pretreatment characteristics

The statistician will report any problems identified to the study chairs, the RTOG Lung Cancer Committee Chair, and if appropriate, to the RTOG Executive Committee.

13.3.2 Analysis for Reporting the Initial Treatment Results (3/2/07)

The usual components of this analysis are:

- tabulation of all cases entered, and any patients excluded from the analysis, with reasons for exclusion
- institutional accrual
- patient accrual rate
- distribution of pretreatment characteristics and other important prognostic baseline variables
- observed results with respect to the endpoints described in Section 13.1.

The differences of CT scan and PET/CT fusion in gross tumor volume, number of involved nodes and dosimetric measures of normal tissue toxicity (mean lung dose, V20, and mean esophageal dose) will be obtained by subtracting each patient’s CT scan measurements from the PET/CT fusion. The distribution of the differences will be graphed to visually assess normality and tested using the Shapiro-Wilk test at a 0.05 significance level. A two-sided one-sample paired t-test will be applied to the differences, if the assumption that the differences are normally distributed is met. Otherwise, the nonparametric Wilcoxon Matched-Pairs Signed-Ranks test will be applied. The test for each measurement will be performed at a significance level of 0.01 because of the Bonferroni multiple comparisons adjustment. If the p-values from any of the above tests are less than 0.01, we conclude that the differences in the CT scan and PET/CT fusion are statistically significant for those measurements.

The percent of nodal locations in agreement will describe the strength of agreement of the two scans regarding the location of involved and uninvolved nodes. For each patient, the percent of nodal locations in agreement as determined by CT only versus PET/CT will be calculated by lymph node stations defined by the AJCC, 6th ed. The mean percent over all patients will combine this measure into a summary statistic for all patients. A 95% confidence interval using the normal approximation for a proportion will be constructed.

The crude elective nodal failure rate in RTOG 9311 was 8%. The statistical power to detect a relevant difference of 50% with the sample size of 48 patients is 19%. This is not sufficient power to test that the rate of elective nodal failure using PET/CT fusion is lower than using CT scan only. However, the rates will be reported.

13.4 Gender and Minorities

In conformance with the National Institutes of Health (NIH) Rev Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have considered differences in prognosis by race and gender. Some investigators have shown gender to be a prognostic factor in NSCLC. However, the RTOG did not show this to be the case in a recent analysis. The study was
designed to test the efficacy under the assumption of the same efficacy across the genders and across the races. The projected gender and minority accruals are:

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Gender</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
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<td>10</td>
<td>38</td>
<td>48</td>
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<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
<td></td>
<td>10</td>
<td>38</td>
<td>48</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Category</th>
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<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
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<tr>
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<td>1</td>
</tr>
<tr>
<td>Black or African American</td>
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<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
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</tr>
<tr>
<td>White</td>
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<td>8</td>
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</tr>
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<td><strong>Racial Category: Total of all subjects</strong></td>
<td></td>
<td>10</td>
<td>38</td>
<td>48</td>
</tr>
</tbody>
</table>

“This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.”
REFERENCES (3/2/07)


Informed Consent Template for Cancer Treatment Trials (English Language)

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have lung cancer that will be treated with radiation therapy.

Why is this study being done?

With positron emission tomography (PET) imaging, cancers appear as “hot spots” that may provide additional information compared with computed tomography (CT) imaging. This information may or may not affect the size and location of the area receiving radiation treatment. The purpose of this study is to determine whether PET with fused CT (PET/CT) changes the size and location of the area receiving radiation treatment compared to planning of the treatment with CT alone. This research will help to determine how often the PET/CT images change the radiation therapy target and how effective the treatment was in controlling your cancer.

How many people will take part in the study?

About 48 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests, or procedures to find out if you can be in the study. These exams, tests, or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- A physical exam
- A biopsy or surgery confirming the presence of lung cancer
- CT of the chest and upper abdomen
- CT or magnetic resonance imaging (MRI) of the brain
- PET or PET/CT scan (which will be used for the study)
- If you are a woman with child-bearing potential, laboratory tests on your blood to exclude pregnancy

During the study …

Your decision to enter this study means that your study doctor will obtain a PET/CT scan and use it for planning radiation therapy for your cancer. Only one PET/CT scan will be obtained. The same scan will be used for both routine staging (determining where your cancer is and is not located) and research purposes. Your doctor may
choose to repeat the PET/CT scan following treatment at his or her discretion. This is not a part of the research study.

PET/CT images are obtained on a combined scanner that is able to obtain both PET and CT images. The PET/CT images will be compared with the CT-alone images (without PET) for research purposes. This comparison will not affect your treatment. Specific management decisions about your cancer care, such as the use of chemotherapy and the number of radiation treatments, will be decided by your physician and are not a part of the research.

You will need these tests and procedures that are part of regular cancer care. They are routine with respect to following your cancer after treatment. This is meant as a guideline and may be modified by your study doctor, depending on the situation.

- Chest CT 3 months after treatment completes, every 6 months for the first 2 years, and yearly thereafter

**How long will I be in the study?**

After completing your treatment, the study doctor will ask you to visit the office for follow-up exams for at least every 3 to 4 months for the first year, every 6 months for the next 2 years, and yearly thereafter. We would like to keep track of your medical condition for the rest of your life. We would like to do this by calling you on the telephone once a year to see how you are doing. Keeping in touch helps us to look at how effective the treatment was for you.

**Can I stop being in the study?**

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop.

It is important to tell the study doctor if you are thinking about stopping so that you can discuss what follow-up care and testing could be most helpful for you. Because this study requires additional imaging only prior to starting your cancer treatment and during follow-up visits with your study doctor after completing treatment, a decision to stop the study implies that you will no longer follow up with your study doctor.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

**What side effects or risks can I expect from being in the study?**

PET imaging involves exposure to radiation from an injection of a radioactive sugar (FDG) for the PET/CT 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 the PET/CT scan. This is about 30% of the allowable annual exposure 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 compared with other everyday risks. If you would like more information about radiation exposure, please speak with your study doctor.

**Risks of Research:** You may have side effects related to the PET/CT scan. Everyone participating in the study will be watched carefully for any side effects. The risk of side effects after the PET/CT scan is very low. There may be a risk of having an allergic reaction to the administered radiation-labeled sugar. However, this reaction has only rarely been observed. Other possible side effects involve the intravenous injection and include bruising or bleeding.

You are likely to experience side effects related to the radiation therapy and chemotherapy treatments. However, these are not part of the research. Your doctor will discuss these potential side effects in detail and answer any questions you might have.
The research portion of this study involves sending your PET/CT and CT-alone images and the radiation treatment plan to an outside facility for review. PET/CT imaging is routinely used for imaging patients with lung cancer and would likely be used to image your cancer whether or not you decide to participate in this study.

For more information about the specific risks of having a PET/CT scan, ask your doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. Although doctors hope that the PET/CT imaging will be more useful against cancer compared to the usual imaging tests, there is no proof of this yet. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:
- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

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. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:
- The local institutional review board (IRB) at your treatment center
- Hospital or University representatives, to complete Hospital or University responsibilities
- Your primary care physician, if a medical condition that needs urgent attention is discovered
- The Radiation Therapy Oncology Group
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Government representatives (such as the Food and Drug Administration or the Office of Human Research Protections) to complete federal or state responsibilities

A group of experts in lung cancer from the RTOG Lung Committee, the RTOG study chairs, and the study statistician will be reviewing the data periodically throughout the study.

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this study?

Because this research study uses one PET/CT scan for both routine and research purposes, there are no additional costs to you or your insurance company because of your participation in this study. Some health plans will not pay for routine health care costs for people taking part in research studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study will not cost your insurance company more than the cost of getting regular cancer treatment.
You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute’s Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the “Clinical Trials and Insurance Coverage” information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, __________________ [investigator’s name(s)], 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(s)] 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]. [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [*Only applies to sites using the CIRB.]

Where can I get more information?

You may call the National Cancer Institute’s Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/
• For NCI’s clinical trials information, go to: http://cancer.gov/clinicaltrials/
• For NCI’s general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant ________________________________

Date _________________________________
APPENDIX II

KARNOFSKY PERFORMANCE SCALE

100 Normal; no complaints; no evidence of disease
90 Able to carry on normal activity; minor signs or symptoms of disease
80 Normal activity with effort; some sign or symptoms of disease
70 Cares for self; unable to carry on normal activity or do active work
60 Requires occasional assistance, but is able to care for most personal needs
50 Requires considerable assistance and frequent medical care
40 Disabled; requires special care and assistance
30 Severely disabled; hospitalization is indicated, although death not imminent
20 Very sick; hospitalization necessary; active support treatment is necessary
10 Moribund; fatal processes progressing rapidly
0 Dead

ZUBROD PERFORMANCE SCALE

0 Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
1 Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).
2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).
3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).
4 Completely disabled. Cannot carry on self-care. Totally confined to bed or (Karnofsky 10-20).
5 Death (Karnofsky 0).
**APPENDIX III**

**AJCC Staging**
**Lung, 6\textsuperscript{th} Edition, 2002**

### Primary Tumor (T)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor.</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma \textit{in situ}</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus,* (i.e., not in the main bronchus)</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor with any of the following features of size or extent: More than 3 cm in greatest dimension; Involves main bronchus, 2 cm or more distal to the carina; Invades the visceral pleura; Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumor nodules in the same lobe; or tumor with a malignant pleural effusion.**</td>
</tr>
</tbody>
</table>

*Note: The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1.

**Note: Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor. In these cases, fluid is non-bloody and is not an exudate. Such patients may be further evaluated by videothoracoscopy (VATS) and direct pleural biopsies. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be staged T1, T2, or T3. |

### Regional Lymph Nodes (N)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed.</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph nodes metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)</td>
</tr>
</tbody>
</table>
# APPENDIX III

**AJCC Staging**  
Lung, 6th Edition, 2002 (con’t)

### Distant Metastasis (M)

**MX**  Distant metastasis cannot be assessed  
**M0**  No distant metastasis  
**M1**  Distant metastasis present

**Note:** M1 includes separate tumor nodule(s) in a different lobe (ipsilateral or contralateral)

### STAGE GROUPING

<table>
<thead>
<tr>
<th>Occult Carcinoma</th>
<th>TX</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
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<tr>
<td></td>
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<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
Before registering your first patient, you must designate three radiation oncologists at your institution who will participate in this study. Any one of these three physicians can be the treating physician. RTOG Headquarters will randomly assign the physicians responsible for the CT-only and PET/CT fusion planning for all patients enrolled through your institution.

No changes in the two physicians responsible for radiation treatment planning are allowed. If a physician leaves the institution or can no longer participate, you must submit a new Radiation Oncologist Designation Form designating a replacement. This replacement investigator must submit his or her own PET/CT contours from an applicable patient (may be a previously submitted case) for review prior to enrolling a new patient (see Section 5.1).

Please fill in the information below and fax this form to RTOG Headquarters: 215-574-0300.

<table>
<thead>
<tr>
<th>Name of Institution</th>
<th>RTOG Inst. No.</th>
<th>NCI Code</th>
<th>Name of Radiation Oncologist</th>
<th>Check here if replacing another physician</th>
</tr>
</thead>
<tbody>
<tr>
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