American College of Surgeons Oncology Group

Z4033

A Pilot Study of Radiofrequency Ablation In High-Risk Patients With Stage IA Non-Small Cell Lung Cancer

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ACOSOG Standard Operating Procedures (SOPs)

For detailed guidelines for the conduct of the study, sites should refer to the following SOPs available on the ACOSOG website at http://www.acosog.org/.

SOP NAME	DESCRIPTION
Data Sub	Data Submission
Death Notice	Notice of Death
Drugs	Procedures related to Drugs
ExtFU	Extended Follow-up
InfCon	Informed Consent Form Procedures
IRB App	Institutional Review Board Approval
OHRP (OPRR) App	Applying for Office of Human Research Protection Assurance
Pat Reg	Patient Registration

Table of Contents

1 Introduction

1.1 Background

Radiofrequency Ablation (RFA) has seen widespread application in the treatment of unresectable liver tumors. More recently, RFA has been considered as an alternative therapy for the treatment of other solid tumors [Curley 1999, Gervais 2000, Dupuy 2001]. Initial experience in using RFA for treatment of lung cancers indicates that the technique appears to be feasible and safe for the ablation of cancers in highly selected patients [Dupuy 2000, Dupuy 2002, Zagoria 2001, Nishida 2002, Kishi 2002, Steinke 2002, Schaefer 2003]. The chief advantage of RFA over standard therapies lies in its ability to heat lung tumor tissue to a lethal temperature, destroying the tumor while incurring minimal damage to surrounding normal lung tissue [Putnam 2000].

In a Phase II study of RFA followed by conventional radiotherapy for patients with inoperable stage I Non-Small Cell Lung Cancer (NSCLC), 24 patients completed treatment with no observed worsening of pulmonary function [Dupuy 2006]. Attempts to further reduce the complications of radiotherapy have included the integration of brachytherapy [Jain 2003].

Although RFA has been used to treat lung tumors in over 500 patients, there remains a need to further define the clinical effectiveness of this modality. To date, there has been no standardization in technique for administering RFA. Dupuy and colleagues [Dupuy 2002] have described the potential clinical applications and frequency of side effects, but long-term outcomes have not been established. A minimally invasive treatment option could potentially improve QOL by controlling local tumor progression and by providing a longer survival compared to current non-surgical standard therapies.

The use of CT nodule densitometry for evaluating and following solitary pulmonary nodules has received considerable attention in the literature. This technique, which utilizes measurement of nodule enhancement following administration of IV contrast, affords a means for determining clinical response to RFA. A recent multi-center study [Swensen 2000] showed 98% sensitivity in detecting malignancy if a threshold of 15 HU enhancements above baseline was used.

Given that the majority of malignant lesions show contrast enhancement, any change in baseline enhancement post-RFA may be relevant to determining the effectiveness of the treatment. As a complementary modality, positron emission tomography (PET) can be used to determine tissue metabolic activity within the lesion. In particular, patients with questionable response to RFA, as determined by CT scan, may benefit from PET scanning by determining the presence of residual disease.

The exact nature of increased activity with respect to tissue healing and tumor growth after RFA is currently unknown. The baseline FDG PET scan will provide quantitative data which are known to predict prognosis. Interval resolution or progression of FDG uptake following RFA could potentially help assess efficacy of therapy or outcome prediction [Vansteenkiste 2004]. Finally, the overall post-inflammatory response following RFA could be studied, particularly in the surrounding normal lung tissue. This will provide data that will allow discrimination between evolving post- inflammatory change, as distinct from recurrence, while the follow-up scans may provide surveillance for the patterns of recurrence over time in these patients.

1.2 Rationale

On the basis of lung cancer statistics, it is estimated that 163,510 people in the United States will be diagnosed with lung cancer in 2005 [ACS 2005]. Lung cancer is the leading cause of cancer death among men and women in the US, with an associated death rate that comprises over 28% of all cancer deaths, surpassing the mortality rates of colon, prostate, and breast cancers combined [ACS 2005]. This fact underscores the importance of developing improved methods to treat this aggressive cancer.

Radiofrequency ablation (RFA*)* is an image-guided, minimally invasive treatment for solid tumors. Patients who are not candidates for traditional lobectomy due to co-morbid medical conditions may benefit from treatment with RFA. Current external beam radiotherapy data in this groups of patients has reported a 2 year survival of 51% [Bradley 2003].We propose to study a group of patients with stage 1A NSCLC who have not been previously treated. This study will provide information on clinical response, overall survival, and progression-free survival.

In addition, the impact of this treatment modality on pulmonary function will be assessed. Pulmonary function will be assessed prior to, and at intervals after, RFA. This will allow each patient to be his or her own control in quantifying any changes after therapy. If proven to be therapeutically effective, RFA could play an important role in the management of patients who are at high risk for operative resection for pulmonary malignancy.

1.3 Objectives

1.3.1 Primary Objectives

- To assess the overall 2 year survival rate after RFA.

1.3.2 Secondary Objectives

- To assess freedom from regional or distant recurrence.

  Definition for regional recurrence: recurrence within another lobe on the same side of ablation, or the ipsilateral mediastinal or subcarinal (N2) nodes.

  Definition of distant recurrence: contralateral, mediastinal (N3) nodes or distant metastatic disease.

- To assess freedom from local recurrence in the ablated lobe.

  Definition for local recurrence: no recurrence in the same lobe or hilum (N1 nodes) or progression at the ablated site after treatment affects have subsided.

- To estimate the number of procedures deemed technical successes.

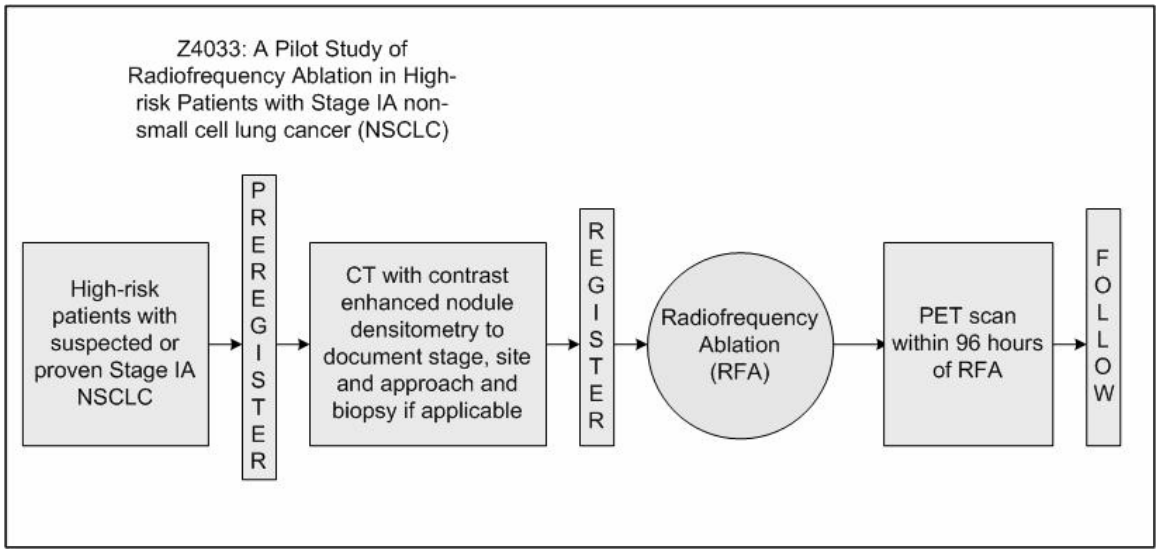
  Definition for technical success: The pertinent captured images from the treatment CT showing RFA electrode placement and the recorded RFA generator parameters (e.g. impedance, current, power, treatment time and maximum intra-tumoral temperature) will be reviewed by the quality control panel to determine technical success.

- To evaluate procedure-specific morbidity and mortality.
- To explore the utility of immediate (within 96 hours) post RFA PET in predicting overall survival and local control.
- To explore the effect of RFA on both short term (3 months post RFA) and long term (24 months post RFA) pulmonary function.

1.4 Study Design and Accrual Goal

This study consists of a single arm pilot trial. The study will accrue 55 patients with the anticipation that 53 patients will be eligible. We estimate that 5 patients per month will be enrolled and conservatively 2-3 of these 5 patients will come from sites that are later deemed "qualified" with a projected enrollment period of 22 months.

1.5 Schema



2 Patient Selection

Each eligibility criterion must be evaluated and **documented** in the patient's medical record. Patient eligibility must be determined by the investigator and confirmed by his or her dated signature.

2.1 Eligibility Criteria

A patient will be eligible for pre-registration to this study only if ALL of the following criteria apply:

Pre-registration Criteria:

1. Patients must have a lung nodule suspicious for clinical stage I NSCLC.
2. Patient must have a mass ≤ 3 cm maximum diameter by CT size estimate: clinical stage IA.
3. Patient must have been evaluated by a thoracic surgeon and been deemed at high risk for a lung resection. NOTE: If the evaluating surgeon is not a member of ACOSOG, then an ACOSOG thoracic surgeon must confirm with dated signature that the patient is high-risk and appropriate for RFA.
4. Patient must have FDG-PET and a CT scan of the chest with upper abdomen within 60 days prior to pre-registration. Patient must have PFTs within 120 days prior to registration.
5. Patient must have an ECOG/Zubrod performance status 0, 1, or 2.
6. Patient must meet at least one major criterion or meet a minimum of two minor criteria as described below:

   Major Criteria

   - FEV1 ≤ 50% predicted
   - DLCO ≤ 50% predicted

   Minor Criteria

   - Age ≥ 75
   - FEV1 51-60% predicted

- DLCO 51-60% predicted
- Pulmonary hypertension (defined as a pulmonary artery systolic pressure greater than 40mmHg) as estimated by echocardiography or right heart catheterization
- Poor left ventricular function (defined as an ejection fraction of 40% or less)
- Resting or Exercise Arterial pO2 $\leq$ 55 mmHg or SpO2 $\leq$ 88%
- pCO2 > 45mmHg
- Modified Medical Research Council (MMRC) Dyspnea Scale $\geq$ 3.

Table 1—*Word Scale (Modified Medical Research Council Scale)*

Grade	Description
0	No breathlessness except with strenuous exercise
1	Breathlessness when hurrying on the level or walking up a slight hill
2	Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level
3	Stops for breath after walking about 100 yards or a few minutes on the level
4	Too breathless to leave the house or breathless when dressing or undressing

7. Patient must not have had previous intra-thoracic radiation therapy.
8. Women of child-bearing potential must have negative serum or urine pregnancy test within 2 weeks of registration.

Registration Activation Criteria:

Patient **must** satisfy **all** of the criteria below to be eligible for full registration to this study:

1. Patient must have histologically or cytologically proven NSCLC, 3 cm or smaller, as determined by the largest dimension on CT lung windows.
2. Patient's tumor must be non-contiguous with vital structures: trachea, esophagus, aorta, aortic arch branches and heart and lesions must be accessible via percutaneous transthoracic route.
3. Patient must have all suspicious mediastinal lymph nodes (> 1 cm short-axis dimension on CT scan or positive on PET scan) assessed by the following to confirm negative involvement with NSCLC (mediastinoscopy, endo-esophageal ultrasound-guided needle aspiration, CT-guided, video-assisted thoracoscopic or open lymph node biopsy).

2.2 Study Guidelines

The following guidelines are intended to assist study physicians in identifying suitable candidates for participation in ACOSOG trials:

- Patients with medical conditions that would render study therapy unreasonably hazardous should not be enrolled in the study.
- Patients who have experienced a prior malignancy should have received potentially curative therapy for that malignancy, and should be cancer free for at least five years from the date of initial diagnosis (Exceptions: patients treated for non-melanoma skin carcinoma or in-situ carcinomas).

3 Study Calendar

	Prior to patient pre-registration	Intervention	24 - 96 hours Post-RFA	M3	M6	M9	M12	M18	M24
REGULATORY									
Obtain informed consent/HIPAA authorization	X								
PROCEDURES									
Med history/ Physical exam	X			X	X	X	X	X	X
ECOG/Zubrod Performance status	X								
Pulmonary Function (incl. DLCO)	X[1]			X					X
Verified NSCLC	X[4]								
RFA[2]		X							
No evidence of N2/N3 involvement[3]	X	X[3]							
RADIOLOGIC TESTS									
CT of chest and upper abdomen with Contrast-Enhanced Nodule Densitometry*	X[1]	X[3]		X	X	X	X	X	X
PET*	X[1]		X[5]		X		X	X	X
SAFETY									
Assess AE's		X	X	X	X	X	X	X	X

[1] PET and CT scans of chest/upper abdomen are performed within 60 days prior to the date of the registration. Contrast-Enhanced Nodule Densitometry is mandatory for all patients, except in the event of a known sensitivity or allergy to the contrast medium, or patient declining the procedure. PFTs are required within 120 days of prior to the date of the pre-registration.

[2] Documentation of the RFA procedure, in the form of a signed and dated dictated procedure note, and pathology, in the form of a signed and dated pathology report must be provided. **NOTE:** RFA must occur within 30 days after patient registration.

[3] If suspicious, N2/N3 adenopathy on radiological test must be assessed histologically before RFA.

[4] Determination of NSCLC and subsequent patient registration may be performed immediately prior to beginning RFA procedure.

[5] The post-RFA 24-96 hour PET scan is for research purposes only. The scan may be a limited scan of the chest from neck to femora. If this PET scan is performed on a PET/CT scanner, it should be conducted without IV contrast. NOTE: Sites will receive reimbursement for this scan for the first 30 patients. 24-96 hour scans for subsequent patients will be optional. All sites will be notified within 24 hours when the first 30 patients have been accrued.

*Follow-up CT and PET scans may be performed on the same day if a PET/CT scanner is used.

4 Registration Procedures

4.1 Pre-registration

Pre-registration is necessary prior to registration. The pre-registration procedures are as follows:

The patient or the patient's legally acceptable representative must provide signed and dated written informed consent prior to pre-registration and prior to beginning any study–related procedure or intervention. Faxed, mailed, e-mailed or verbal consents are NOT ACCEPTABLE.

The patient or the patient's legally acceptable representative must also provide signed and dated consent to the use of their Protected Health Information (this may be incorporated into the informed consent document). PLEASE NOTE: only US sites responsible for upholding HIPAA requirements are required to obtain signed consent for use of Protected Health Information.

Prior to pre-registering a patient to study, the physician must verify that all of the pre-registration eligibility criteria noted in the protocol have been met. **No waivers or exemptions to any eligibility criterion will be granted. All eligibility criteria must be fully documented in patient's chart. Do not use any Case Report Forms (CRFs) as source documents.**

Pre-registration is done through the ACOSOG website's Patient Registration function. **Please note: you must be logged in as an ACOSOG member to access this function. Any lapse or failure to complete documentation regarding membership, qualifications/skills or IRB-related issues will prevent registration from occurring.**

At the time of pre-registration, the ACOSOG Patient Registration program will prompt the user to provide the following items:

- The ACOSOG or CTEP ID number of the physician registering the patient
- The ACOSOG or CTEP ID number for the institution at which the patient is being registered
- The patient's initials
- A local identifier for the patient (typically a medical record number or a social security number. In the event of institutional policy against releasing such information, the site may create its own local identifiers for the patient).
- The ACOSOG patient registration program will validate physician and site credentials before permitting registration to proceed. Once pre-registration is completed, a unique ACOSOG patient ID number will be generated, along with a randomly generated 8-digit "token number."

4.2 Registration

After confirmation of full eligibility, use a touch-tone telephone to access the automated Interactive Voice Response (IVR) system for registration by calling 866-488-0651 (toll-free) or 919-668-7126. The person placing the registration call responds to pre-recorded voice requests using the touch-tone keypad. The caller will be prompted to provide the token (number) given during the pre-registration process. Upon verification of the token number, the patient will be registered.

If a patient is found to be ineligible during RFA procedure, the token should be canceled using the CANCEL TOKEN procedure found on the Patient Registration page of the ACOSOG web site. NOTE: in the event that a token is cancelled, the patient is not considered to be an ACOSOG study subject, and the site should not submit any Case Report Forms for that patient.

5 Intervention

This section gives an overview of the intervention and procedures to be used in this study and how they are to be applied.

5.1 Preparation

A Radionics CC-1 [Radionics Inc, Burlington, MA] radiofrequency generator and perfusion pump will be used. A Radionics cluster Cool-tip electrode [Radionics Inc, Burlington, MA] with variable lengths (10, 15, 20 cm) and fixed active tip exposure (2.5 cm) will be used.

To reduce potential complications of sedation-induced nausea and aspiration of gastric contents, all patients are treated after an overnight fast. Patients on extensive medications, in particular hypertension and cardiac medications may take these medications in the morning with a small quantity of water. Insulin dependent diabetic patients should administer half of their usual morning insulin dose. An abridged physical is performed outside the procedure suite and an intravenous line is placed. Thirty minutes prior to and after the commencement of the procedure all patients are given intravenous conscious sedation (fentanyl, versed, etc.) Droperidol can be used for its sedative and anti-emetic effects (Parkinson's patients should not receive droperidol as this may exacerbate their symptoms).

CT-guidance is initiated and an image is taken with the spinal needle in place to identify proper table position and needle angle. Repositioning can be performed with the spinal needle if necessary. A small skin incision is made at the correct skin entry site by plunging a #11 scalpel blade 1-2 cm into the subcutaneous tissues.

5.2 Electrode Placement and Treatment

Note: CT images of the treatment electrode placement within the target lesion must be obtained prior to each activation of the RF generator. These images should also be among the images transferred to ACRIN and archived. These images are necessary to ascertain the technical success and quality of treatment

The RF electrode is placed through the skin and pleura to a length corresponding to one-half to two-thirds the distance to the target lesion. A CT image is obtained and the RF electrode angle in the x, y and z plane is corrected as necessary. For pleural-based masses, a shorter RF electrode is employed. Placement of the electrode within the target tumor in these cases may need to be performed without initial superficial positioning since superficial placement from a lateral position may result in protrusion of the electrode, thereby obstructing patient placement into the gantry. A tandem guiding needle may also be used, whereby the RF electrode is placed into the mass immediately following confirmation of the tandem guiding needle's position.

For lesions smaller than 2 cm in diameter, central and distal positioning of the RF electrode is usually adequate for the first ablation, with subsequent tandem ablation zones performed during more proximal positioning. When possible, the target lesion should be entered along its longitudinal axis to allow for this type of sequential overlapping tandem ablation during electrode withdrawal. For lesions larger than 2 cm in diameter, multiple overlapping ablation zones may need to be performed to insure adequate thermocoagulation of the target lesion.

The radiofrequency electrode contains an internal thermocoupler for temperature measurement. The electrode will be connected to a Radionics CC-1 radiofrequency generator and perfusion pump [Valley Lab, Boulder, CO] Internal cooling of the electrode (tip temperature $<20^{o}$ C) will be performed with continuous infusion of ice water at 80ml/min with the accompanying perfusion pump.

At the end of each treatment the perfusion will be stopped and the maximum temperature recorded. The quantity of RF energy cannot be standardized for each individual tumor as the heat capacity of any given tumor may vary based on tumor histology, local blood flow and previous treatments. At least one RF treatment will be created with the maximal allowable current given the impedance of the system (typical range: 1100-2000mA) for no more than 12

minutes. After the 12 minute period, the internal perfusion of the electrode will be stopped and the current will be turned off.

5.3 Temperature and Impedance Monitoring

The maximal intratumoral temperature will be recorded from the device to ensure adequate thermocoagulation, an intratumoral temperature greater than 60^{o} Celsius must be obtained at the end of the treatment. If the temperature exceeds 60^{o}C, the RF electrode will be withdrawn in increments of 1cm up to the length of the active tip (i.e., 2.5 cm). If the temperature falls below 60^{o} C and the RF electrode is still within the tumor mass as determined by imaging, another 12 minute treatment will be performed at the new position. If after the first 12-minute treatment the maximum intratumoral temperature does not exceed 60^{o} C, the electrode will be withdrawn 5mm and an additional 12-minute treatment will be performed at the same position. This can be repeated for a maximum combined duration of 36 minutes (i.e., 3 treatments) for any given tumor.

A single 12-minute treatment with a cluster electrode can create a diameter of thermocoagulation of approximately 3.5-7.0cm, depending upon regional tissue perfusion. The treatment current in milliamps, power in watts, impedance in ohms, as well as duration and maximal intratumoral temperature for each treatment will be recorded.

5.4 Electrode Removal and Post-intervention Evaluation and Treatment

After the target tumor is treated, the RF electrode is removed and a CT image is obtained to evaluate for a pneumothorax. Large pneumothoraces can be evacuated at this time with chest catheters and wall suction. Smaller asymptomatic pneumothoraces can be followed with chest radiographs. In the latter circumstance, patients will be administered 100% oxygen via a non-rebreathing mask and chest radiograph will be obtained immediately, to be followed by a 2-hour follow-up radiograph.

Evidence of an increasing pneumothorax on this 2-hour follow-up radiograph typically necessitates chest catheter placement. Once a chest catheter has been placed and there is radiographic documentation of pneumothorax resolution, the patient may be managed per institutional guidelines.

All patients are observed for at least two hours post-procedure, and interval follow-up imaging is scheduled upon discharge.

5.4.1 Post-RFA PET Scan

A post-intervention FDG-PET scan will be performed within 24-96 hours of completion of the RFA procedure. The post-RFA 24-96 hour PET scan is for research purposes only. The scan may be a limited scan of the chest from neck to femora. If this PET scan is performed on a PET/CT scanner, it should be conducted without IV contrast.

Sites will receive reimbursement for this scan for the first 30 patients. 24-96 hour scans for subsequent patients will be optional. All sites will be notified within 24 hours when the first 30 patients have been accrued.

6 Follow-up

Protocol follow-up will be performed at 3, 6, 9, 12, 18, and 24 months as required by the Study Calendar.

Patients will be monitored for local recurrence, regional recurrence and distant recurrence for two years as required by the Study Calendar. Patients also will be monitored for additional primaries, with histological confirmation whenever possible.

7 Evaluation of Outcomes

7.1 Outcomes Assessment

Local Recurrence

Local recurrence is indicated when a follow-up examination shows recurrence in the same lobe or hilum (N1 nodes) or progression at the ablated site (local progression), visible on radiological images (nodule-enhanced Chest CT; see section 9.1) after treatment effects have subsided. Since scarring may occur adjacent to the ablation site, a CT scan will be obtained at 3 months. This will form the baseline study against which local recurrence will be judged.

Regional Recurrence

Regional recurrence is indicated when a follow-up examination shows recurrence within another lobe on the same side of ablation, or the ipsilateral mediastinal or subcarinal (N2) nodes, visible on radiological images (nodule-enhanced Chest CT; see section 9.1).

Distant Recurrence

Distant recurrence is indicated when a follow-up examination shows recurrence within a contralateral lobe, contralateral mediastinal (N3) nodes or distant metastatic disease, visible on radiological images (nodule-enhanced Chest CT; see section 9.1).

7.2 Survival

Patients will be followed for 2 years for overall survival.

7.3 Pulmonary Function Tests

Pulmonary function tests with diffusion capacity will be obtained before pre-registration and at 3 and 24 months after the RFA procedure.

8 Adverse Event Reporting

Adverse Event (AE)

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.

8.1 Adverse Event Reporting

The prompt reporting of adverse events is the responsibility of each investigator, nurse or clinical research associate engaged in clinical research. Any investigator who is dubious about whether a particular adverse event should be reported should contact the ACOSOG Coordinating Center at (919) 668-8191 for assistance.

The following steps should be taken to initiate an adverse event report:

1. Identify the event
2. Grade the severity of the event.
3. Determine attribution of the adverse event, is the event related to the medical treatment or surgical procedure?
4. Determine if the adverse event is expected or unexpected
5. Determine if the event should be reported to the NCI as an expedited report via the Adverse Event Expedited Reporting System (AdEERS) or as a routine report on the ACOSOG case report form.

All AEs including those submitted to ACOSOG via AdEERS must be recorded in the medical records, and must be reported through the AE CRF.

Attribution

Attribution is the determination of whether an adverse event is related to investigational medical treatment or procedure.

Attribution categories are:

Definite	The adverse event is clearly related to the treatment or procedure
Probable	The adverse event is likely related to the treatment or procedure
Possible	The adverse event is may be related to the treatment or procedure
Unlikely	The adverse event is doubtfully related to the treatment or procedure
Unrelated	The adverse event is clearly NOT related to the treatment or procedure

Grade

Grade is used to denote the severity of the adverse event. An AE is graded using the following categories ONLY if the term does NOT appear in the current version of the Common Terminology Criteria for Adverse Event Reporting (CTCAE v. 3.0):

1	Mild adverse event
2	Moderate adverse event
3	Severe adverse event
4	Life-threatening or disabling adverse event
5	Fatal adverse event

For terms listed in the CTCAE, the grade is also recorded as 1, 2, 3, 4, or 5; however, the definition of the various grades will be specific to the term being used.

8.2 NCI Common Terminology Criteria for Adverse Events

This study will collect adverse events using the current version of the Common Terminology Criteria for Adverse Events Version 3.0. (CTCAE v.3.0) An electronic version of the CTCAE may be accessed through the web at: http://ctep.cancer.gov/forms/CTCAEv3.pdf.

The CTCAE provides a descriptive terminology that is to be used for adverse event reporting. A grading (severity) scale is also provided in the CTCAE for each adverse event term.

8.3 Expected Adverse Events

The following AEs associated with Radiofrequency Ablation (RFA) are anticipated. Refer to the NCI CTCAE for coding criteria of AEs.

The following list provides the expected adverse events:

- Pneumothorax
- Hemorrhage/Bleeding associated with (RFA) surgery, intra-operative or postoperative
- Injection site reaction/extravasation changes
- RFA-related damage to neighboring structures
- Hemoptysis (bronchial or pulmonary hemorrhage)
- Burn (second degree or greater skin burn at electrode and grounding pad sites)
- Respiratory failure (Pulmonary-Other)
- Empyema

8.4 Routine Adverse Event Reporting

Expected and Unexpected Adverse Event Reporting through Case Report Form

All grade 3-5 expected and unexpected adverse events occurring during the study intervention and within 30 days following to the completion of the study will be reported using the Adverse Event case report form (AE CRF). Events (grade 3-5) related to the radiofrequency ablation procedure will be reported to 24 months on the AE CRF.

8.5 Expedited Adverse Event Reporting

What to Report

An expedited report is required during the study intervention and within 30 days following the end of study intervention regardless of attribution for all unexpected Grade 4 (life-threatening) adverse events and all (unexpected and expected) Grade 5 (fatal) adverse events regardless of attribution.

All deaths within 30 days of the date of the intervention regardless of attribution must be reported. Any death $\geq$ 30-days attributed to study intervention (possible, probable or definite) should be reported within 10 working days of knowledge of event.

UNEXPECTED EVENT			EXPECTED EVENT		
Grades 2-3 Regardless of Attribution	Grade 4 Regardless of Attribution	Grade 5 Regardless of Attribution	Grades 2-3 Regardless of Attribution	Grade 4 Regardless of Attribution	Grade 5 Regardless of Attribution
Adverse Event Expedited Reporting NOT required	Expedited Report within 10 working days	Report by phone to ACOSOG within 24 hrs of knowledge of event	Adverse Event Expedited Reporting NOT required	Adverse Event Expedited Reporting NOT required	Report by phone to ACOSOG within 24 hrs of knowledge of event

(Grade 1-Adverse Event Expedited Reporting is NOT required).

How to Report

AdEERS reports are via electronic submission through the AdEERS web application (http://ctep.cancer.gov/reporting/adeers.html). *Single Agent or Multiple Agents* paper templates are to be used *only* if the AdEERS Web-based application is unavailable. The templates are available at: http://ctep.cancer.gov/reporting/adeers.html. Completed templates should be faxed to the NCI at 301-948-2242.

When to Report

Once the investigative site becomes aware of the event, it should be reported within ten (10) working days. All fatal (Grade 5) adverse events should also be reported by telephone to IDB at 301-230-2330 and to ACOSOG at 919-668-8191 within 24 hours of the event.

Where to Report

For electronic submission: Use the AdEERS web application

Additional information: By mail: Investigational Drug Branch (INB)
PO Box 30012
Bethesda, Maryland 20824

For paper submission: By fax: 1-301-230-0159

Telephone report to NCI is available 24 hrs a day by calling 301-230-2330 (voicemail recorder after hours 5:00pm-9:00am Eastern Time)

A telephone report to ACOSOG is available 24 hours a day by calling 919-668-8400 (voicemail recorder after hours 5:00pm to 9:00am Eastern Time).

To Local IRB: All expedited reports must be submitted to your local Institutional Review Board (IRB). However you should abide by your local IRB's policies and procedures in reporting adverse events.

9 Imaging

Note: CT images of the treatment electrode placement within the target lesion must be obtained prior to each activation of the RF generator. These images should also be among the images transferred to ACRIN and archived. These images are necessary to ascertain the technical success and quality of treatment

Required imaging for Z4033 will consist of the following:

- CT of chest and upper abdomen utilizing Contrast-Enhanced Nodule Densitometry prior to patient registration and again at 3, 6, 9, 12, 18, and 24 months post-RFA.
- PET scan prior to patient registration, within 24-96 hours following completion of RFA procedure, and at 6, 12, 18, and 24 months post-RFA.

Please find details of imaging technique, quality assurance measures, and image submission guidelines listed below. The immediate post-RFA PET scan will be supported by funding from the National Cancer Institute's Cancer Imaging Program (CIP).

9.1 CT Imaging Procedures

9.1.1 Spiral CT

Protocol for Scanning (General Parameters)

1. Scout: Noncontrast sequence through entire chest with kV at least 120 or higher; mA at least 200 or higher; detector collimation at least 3 mm or smaller; pitch 2 or smaller; slice thickness 3 mm or smaller; reconstruction interval 30-60% overlap; reconstruction filter; bone algorithm; suspended maximal inspiration.
2. Mandatory* Contrast Nodule Densitometry: Nodule/post ablation site densitometry with kV at least 120 or higher; mA at least 220 or higher; detector collimation at least 1.5 mm or smaller (1 mm or less preferably); pitch 2 or smaller; slice thickness 1.5 mm or smaller; reconstruction interval 30-60% overlap; reconstruction filter standard algorithm; suspended maximal inspiration. Techniques include:
   - Display Field of View (DFOV) individualized per patient.
   - Contrast-Omnipaque or equivalent 350 < 100 lbs.: 100 cc; 100-200 lbs.: 125 cc; >200 lbs.: 150 cc at a rate of 2 cc/sec intravenous injection.
   - 1 mm collimation through nodule/treated lesion pre- and post-contrast at 0 seconds and 45, 90, 180, and 300 seconds following contrast injection.
   - Region of interest (ROI) determinations and time density curve creation.
   - Determination of maximum contrast enhancement compared to baseline.

**Note: Contrast Nodule Densitometry must be performed, unless contraindicated due to the patient's medical condition, or unless the patient declines the Contrast Nodule Densitometry procedure.*

9.1.2 Newer Generation Multidetector CT

Protocol for Scanning (General Parameters)

1. Scout: Noncontrast sequence through entire chest with kV at least 120 or higher; mA at least 200 effective or higher; 0.75 mm detector collimation; 10.5 mm table travel; 0.5 seconds gantry rotation; slice thickness 3 mm or smaller; reconstruction interval 30-60% overlap; reconstruction kernel B45F; suspended maximal inspiration.
2. Mandatory* Contrast Nodule Densitometry: Nodule/post ablation site densitometry with kV 120; mA at least 250 or higher; 0.75 mm detector collimation; 6.1 mm table travel; 0.5 seconds gantry rotation; slice thickness 1.5 mm or smaller; reconstruction interval 30-60% overlap; reconstruction kernel B45F; suspended maximal inspiration.
   - Display Field of View (DFOV) individualized per patient.
   - Contrast-Omnipaque or equivalent 350 (< 100 lbs.: 100 cc; 100-200 lbs.: 125 cc; >200 lbs.: 150 cc at 2 cc/sec intravenous injection with 0.75 mm collimation through nodule/treated lesion pre- and post-contrast at 0 seconds and 45, 90, 180, and 300 seconds following contrast injection.
   - Region of interest (ROI) determinations and time density curve creation.
   - Determination of maximum contrast enhancement compared to baseline.

**Note: Contrast Nodule Densitometry must be performed, unless contraindicated due to the patient's medical condition, or unless the patient declines the Contrast Nodule Densitometry procedure.*

9.1.3 Quantitative Measurements

Target lesion will be measured in three dimensions on all initial and follow-up CT scans.

Any growth of the target lesion 1.25 times any dimension obtained at the 3-month baseline CT (as determined on lung windows) scan or on subsequent CT scans will be considered suspicious for recurrence and require biopsy. (If contrast enhancement performed: Any mass lesion measuring greater than 9mm in the treatment field that enhances 15HU within 1 minute after contrast injection will also be considered suspicious for recurrence.)

CT-guided fine needle aspiration biopsies will be performed when clinically appropriate for all patients with changes in the treated nodule suspicious for recurrence.

9.2 PET Imaging

9.2.1 PET Imaging Equipment

A dedicated BGO, LSO, or GSO PET scanner or hybrid PET/CT scanner is mandatory. PET scanners with NaI detectors and coincidence cameras are not acceptable. 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. It is strongly encouraged that all of the serial PET studies for this trial be done at the same institution and on the same scanner (or same type of scanner), using the same dose, imaging times and reconstruction parameters.

9.2.2 Patient Preparation and FDG Injection/Uptake

Patients must fast for a minimum of 4 hours prior to the injection of FDG for the PET scan. Blood glucose will be measured and recorded prior to the 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, in compliance with applicable local, state, and federal regulations.

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).

9.2.3 FDG PET Imaging Parameters

Emission imaging will be started approximately 50-70 minutes after FDG injection. The time from injection of FDG to start of imaging should be maintained as constant as possible on serial PET studies. The patient will empty his/her bladder immediately before the acquisition of images. The patient will be scanned supine and with arms up, if possible. The scanned regions will be from the upper/mid-neck to the proximal femora.

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 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.

PET image reconstruction will be done using manufacturer provided algorithms. For PET/CT units image reconstruction should be done using vendor provided reconstruction algorithms utilizing the CT dataset, and utilization of OSEM reconstruction is recommended.

9.2.4 Image interpretation and analysis

Interpretation will be qualitative guided by semi quantitative results (determination of the maximum standardized uptake value [SUV-max] utilizing vendor-provided software). The SUV will be normalized to body weight. No films will be utilized for image interpretation as the film exposure settings may affect visual interpretation. In general, lesions that are metabolically active and >1.5 cm in largest diameter should have a maximum SUV of greater than 2.5 to be considered as tumor. The nuclear medicine physician should visually identify 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 the CT scan. A two-dimensional or three-dimensional region of interest centered on the maximum-value pixel will be drawn, and the manufacturer's algorithm will be used to calculate the maximum SUV within this region; this value will be reported as the SUV-max. If two or more regions of interest are analyzed, the one with the higher SUV-max will be reported for the purposes of this protocol. In addition, on post-RFA PET scans, a separate measurement of the SUV-max of the rim of increased activity surrounding the ablation site should be performed, if a visible rim is seen on the images.

9.2.5 Post-RFA PET scans

The post-treatment PET scan is to be done according to the same specifications described in detail above (Section 9.2.3). The PET scan needs to be done within the same institution on the same scanner (or, if this is not feasible, on the same model PET scanner) used for the pre-treatment PET. A post-treatment PET scan will be done 24-96 hours following completion of RFA, and again at 6, 12, 18, and 24 months after the completion of RFA.

NOTE: The post-RFA 24-96 hour PET scan is for research purposes only. The scan may be a limited scan of the chest from neck to femora. If this PET scan is performed on a PET/CT scanner, it should be conducted without IV contrast.

Sites will receive reimbursement for this scan for the first 30 patients. 24-96 hour scans for subsequent patients will be optional. All sites will be notified within 24 hours when the first 30 patients have been accrued.

Response assessment utilizing both the CT and PET data will be done. For qualitative assessment of the PET images, response criteria similar to those previously described by MacManus, et al. will be used [MacManus MP, Hicks RJ, Matthews JP, et al. 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*. 21: 1285-92, 2003]. Visual assessment of response will be used, as follows:

- **Complete metabolic response:** No evidence of FDG uptake in the tumor or activity similar to that in the mediastinum

- **Partial metabolic response:** Appreciable reduction in the intensity of tumor FDG uptake or tumor volume apparent to the nuclear medicine physician when pre- and post-treatment PET scan are compared, with no evidence of disease progression
- **No metabolic response:** No appreciable reduction in the intensity of tumor FDG uptake or tumor volume apparent to the nuclear medicine physician when pre-and post-treatment PET scans are compared, with no evidence of disease progression
- **Progressive metabolic disease:** Appreciable increase in the intensity of tumor FDG uptake or tumor volume apparent to the nuclear medicine physician when pre- and post-treatment PET are compared or with evidence of disease progression at other sites

The qualitative visual assessment of response may be guided by the semi qualitative analysis as follows. A complete metabolic response is defined as resolution of abnormal FDG uptake (SUV-max <2.5 in lesion area >1.5 cm). Partial metabolic response is defined as a greater than 20% decrease in SUV-max from the baseline scan or significant decrease in size of lesion that is still metabolically active. Stable metabolically active disease is defined as an SUV-max decrease less than 20% but no increase greater than 20%. Progressive metabolically active disease is defined as identification of new lesions, increase in lesion size, or interval increase in SUV-max by.>20%. The interpretation of the scans will be done with full knowledge of the CT findings on dedicated scanners and with the accompanying CT for PET/CT as this improves the accuracy of the interpretation of the PET study.

The finding of either no metabolic response or of progressive metabolic disease on the 6-month post-RFA or subsequent PET scans will be considered suspicious for recurrence and require biopsy when clinically appropriate.

9.3 Image Submission

Digitally generated diagnostic images can be transmitted to the ACRIN Data Management Center *(DMC)* via FTP directly to the image archive. The FTP site is located at ftp://xray.acrin.org or ftp://206.137.103.34. For each transmission a new folder for your institution and sub-folders for each corresponding exam must be created. Images are to be transferred into those folders. An e-mail verifying the transfer and its contents including the name and number of exams as well as image count for each should be sent to both ***(amurray@phila.acr.org)*** and ***(alevering@phila.acr.org).*** Please verify the transmission by examining the folders to make certain that all the images were received.

Note: For digital images the full set of digital image data will be considered acceptable and that while processed images such as jpeg format images, may be provided they will not be considered sufficient or compliant with this protocol.

Please note that the header record on DICOM formatted image data, which often contains information identifying the patient by name, MUST be scrubbed before the image is transferred. This involves replacing the Patient Name tag with the Institution ID or number, replacing Patient ID tag with the ACRIN case number and put the study number into the Other Patient ID tag. This can either be done by software present at the institution or software, which is available from the ACRIN DMC (please contact Rex Welsh 215-574-3215 for information).

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 DMC to transfer to the image archive. Please contact the ACRIN DMC prior to sending the media to confirm compatibility.

All media will be retained by the ACRIN DMC unless otherwise requested and return packaging and postage is provided. Mailed images on CD should be addressed as follows:

ACRIN Image Archive

ACRIN 6661 Images

American College of Radiology

1101 Market Street, Suite 1400

Philadelphia, PA. 19107

Images stored on the ACRIN DMC image archive will be routed to other sites involved using either FTP or CD-ROM where appropriate for purposes of secondary interpretation.

10 Data Considerations

The clinical site should access the case report form (CRF) section of the ACOSOG web site, http://www.acosog.org to obtain blank CRFs for data submission to the ACOSOG Coordinating Center. Each CRF page needed for this study can be found on the ACOSOG web site as a Portable Document Format (PDF) file. The CRFs can be printed directly from the browser used to access the ACOSOG web site. The CRFs also can be saved as a file, and then printed.

10.1 Case Report Form Completion and Submission Guidelines

This trial will utilize the Mayo Clinic Cancer Center Remote Data Capture system for data entry. You can access the system through the following URL https://ncctg.mayo.edu/acosog. Instructions on how to use this system are located on the web site under the header "instructions". The Clinical Research Associate who will be responsible for data entry will need to apply for a user ID and password prior to use. Please contact the Disease Site Coordinator for details.

10.2 Patient Data Quality Control

All data received via case report forms will be subjected to various ACOSOG validation and quality-control measures. Issues arising from inaccurate, discrepant or incomplete data will be communicated to participating sites on a regular basis, along with patient status summaries.

Any data submitted on case report forms is subject to audit against the patient's source documents.

Consistent failure to complete and submit data in a timely fashion may subject a participating site to sanction up to and including the suspension of participation in the study.

10.3 Patient Data Review

Patient data will be reviewed for patient eligibility and general protocol compliance by the Study Chair and/or designees.

10.3.1 Study Endpoint Evaluation

Patient Data Review for this protocol will incorporate centralized review of study endpoints, including response evaluation and survival as described in Section 7. These necessary and important images are critical to ascertain the technical success and quality of treatment and will also be used to qualify sites and monitor quality.

10.3.2 Quality Control of RFA and Images

Quality Control will be established to monitor the protocol compliance with the RFA procedure. The first 20 sites that are eligible (regulatory submission complete, IRB approval, contract executed, etc.) will be allowed to initially enroll 2 patients each. The Study Chair and Study Co-Chair, will review after each enrollment, the pertinent images from the treatment CT showing the RFA electrode placement and the RFA generator parameters (e.g. impedance, current, power, treatment time and maximum intra-tumoral temperature). In addition, the contrast CT studies will be analyzed by a panel of 2 individuals from the protocol team including a radiologist with thoracic imaging expertise for an additional 5 quality control measures: adequacy of contrast administration, proper field of view, collimation, appropriate tumoral coverage and lack of patient motion.

Technical successes and failures will be recorded and any deviations will be communicated to the site investigator by the Study Chair. If both cases are deemed technical successes the site

will be deemed qualified and may continue to enroll patients. If one procedure is a technical success and the other is a technical failure the expert panel will determine whether the site is qualified based on the nature of the failure. A total of 2 technical failures from any one site will result in termination of enrollment privileges.

11 Statistical Considerations

11.1 Statistical Considerations

See Section 10.3.2 for the quality control process for determining qualified sites. The first 2 patients (whether deemed technical successes or not) from all qualified sites will be included in all efficacy endpoints, including the proportion of patients alive at 2 years.

11.2 Primary Endpoint

The primary endpoint is overall survival at 2 years. The RFA procedure will not be considered of interest if the 2 year survival rate <= 30% and will be considered of interest if it is > 50%. (The overall 2 year survival rate for RT in a similar population was reported to be 51%, [Bradley, 2003]. Due to the need to follow all patients for 2 years before assessing them for this endpoint of interest we will not perform an interim analysis for this endpoint. If 22 or more of the 55 evaluable patients from a site deemed qualified are alive at 2 years this procedure will be considered promising for further development. If 21 or less are alive at 2 years, this procedure will be considered ineffective in this patient population.

Assuming that the number of deaths is binomially distributed, the significance level is 0.07 and the probability of declaring that this regimen warrants further studies (i.e. statistical power) under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true 2 year overall survival rate is:	30%	35%	40%	45%	50%
then the probability of declaring that the procedure warrants further studies is	.07	.26	.55	.81	.95

11.3 Secondary Endpoints and Analysis

The overall time to local failure will be defined as the time from registration to documentation of local failure. The distribution of time to local failure will be estimated using the cumulative incidence method accounting for distant recurrence and death as a competing risk. Local failure will be defined as: recurrence in the same lobe or hilum (N1 nodes) or progression at the ablated site after treatment affects have subsided.

The overall time to recurrence is defined as the time from registration to documentation of disease recurrence. If a patient dies without a documentation of disease recurrence, the patient will be considered to have had tumor recurrence at the time of their death unless there is sufficient evidence to conclude no recurrence occurred prior to death. The distribution of time to recurrence will be estimated using the method of Kaplan-Meier.

The proportion of technical success will be estimated by the number of patients with a RFA procedures deemed a technical success divided by the total number of RFA procedures attempted from the qualified sites. Confidence intervals for the true success proportion will be calculated using the EXACT method.

The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine any adverse event patterns. This will be done overall and for just those sites deemed qualified after expert review.

To explore the impact of imaging techniques of RFA on overall survival and recurrence rates, a cox proportional hazards model will be constructed. Lesion growth, CT-densitometry measurements and FDG-PET activity (in early and follow-up setting) will be used. This analysis will be exploratory in nature as sample sizes will be relatively small.

To explore the effect of RFA pulmonary function, the difference in pulmonary function from baseline (pre RFA) and 3 months post RFA will be computed for each patient and a Wilcoxon Sign Rank Test or paired t test will be computed (whichever is more appropriate based on the distribution of the data) to evaluate if the overall change is significantly different from 0. This will also be done at 24 months post RFA to assess the more long term effects of RFA on pulmonary function. A sensitivity analysis will be conducted to evaluate the effects of any missing data on the overall findings.

12 Regulatory and Ethical Considerations

12.1 ACOSOG Membership

The investigator intending to register a patient to this study (radiologist or thoracic surgeon) must be a member in good standing of the American College of Surgeons Clinical Oncology Group (ACOSOG). The procedures for obtaining active status in ACOSOG are described in the membership information found on the ACOSOG web site at http://www.acosog.org. Without prejudices ACOSOG will facilitate membership for surgeons/radiologists who are interested in being a PI on this study.

NOTE: The thoracic surgeon responsible for confirming the patient's appropriateness for RFA must be an ACOSOG member.

12.2 NCI Investigator Registration

All enrolling and treating investigators must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (Form FDA 1572 with original signature, current CV, Supplemental Investigator Data Form with original signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch. These forms, along with completion and submission instructions, are available on the ACOSOG web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30AM and 4:30PM Eastern time.

12.3 Clinical Site Eligibility

The clinical site must be formally part of or affiliated with an institution that has active status in ACOSOG; or if this study is open for registration from other cooperative groups, the institution must have active status in the group permitted to register to this study. If the institution has joined ACOSOG, notification of the successful application must have been issued at least 7 days prior to the first attempted registration of a patient.

12.4 OHRP Considerations

An ACOSOG member must enroll patients at clinical sites (institutions) that have a valid Federalwide Assurance (FWA) number from the United States Office for Human Research Protections (OHRP). If the clinical site does not have such an assurance, the clinical site must apply and obtain an assurance before patients can be enrolled to ACOSOG studies.

Unaffiliated Investigator Agreements (UIAs) are needed from investigators who independently accrue patients on ambulatory protocols outside an institution (e.g., in private practice) but who rely on an institution's IRB for review of ACOSOG protocols.

Information on applying for a FWA may be obtained from the ACOSOG Coordinating Center, by referring to ACOSOG SOP "Applying for OHRP Assurance", or by directly contacting OHRP.

12.5 Institutional Review Board Approval

It is the investigator's responsibility to ensure that this protocol is reviewed and approved by the appropriate IRB. Each clinical site must obtain a letter of approval from the IRB (full board review) prior to screening and registering patients to this study, as defined by the following:

- Federal Regulatory Guidelines (Federal Register Vol. 46, 8975, January 27, 1981 as amended in Federal Register Vol. 56, 28029, June 18, 1991 and in Federal Register Vol. 66, 56775, November 13, 2001).
- Office of Protection for Research Risks Report: Protection of Human Subjects (Code of Federal Regulations Title 45, Part 46).

The IRB also must review and approve the site's informed consent document and any other written information provided to the patient prior to its use.

Participating investigators are required to submit a copy of the IRB document indicating approval of the protocol and the consent form, as well as a copy of the IRB-approved consent form, prior to registering the first patient. For instructions on the submission of these documents please refer to the IRB Approval SOP (IRB App) found on the ACOSOG web site at http://www.acosog.org/.

If, during the study, it is necessary for ACOSOG to amend either the protocol or informed consent document, the investigator will be responsible for ensuring the IRB reviews and approves the amended documents. IRB approval of the amended informed consent document must be obtained before new patients consent to participate in the study using this version of the consent.

12.6 Informed Consent

12.6.1 ACOSOG Preparation of the Model Informed Consent Document

The NCI's Informed Consent Template, originally drafted in 1998, has been updated.

Representatives from the Cooperative Groups, NCI's Central IRB (CIRB), NCI staff/contractors including a literacy expert, and patient advocacy representatives from the CIRB, the Director's Consumer Liaison Group and CARRA (Consumer Advocates in Research and Related Activities) participated in a Working Group that reviewed and revised the existing template.

Changes requested by FDA and OHRP have also been incorporated in the final document. The revised version of the template is posted on the web at:

http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/page3

The NCI requires that this template be used in the creation of model informed consent documents for all ACOSOG studies.

12.6.2 Adaptation of the Model Informed Consent Document

For each protocol, the ACOSOG provides a model informed consent document in a file form that can be downloaded for inclusion into a chosen word processing system. The Informed Consent SOP (InfCon SOP) discusses how to adapt the model informed consent document for local use. *This model informed consent has been approved for use by the DCT/NCI, and is the only consent document approved for this study.* **All required elements and NCI required text must be included when adapting the model informed consent to include site-specific text requirements.** Local IRB adaptations and editorial changes of this document are allowed as long as the meaning or intent of any section is not changed.

When the model informed consent for an ACOSOG protocol is adapted to local requirements, it is the responsibility of that institution to ensure that protocol procedures, especially risks, adverse events, and treatment choices, are fully and accurately represented in the local informed consent to be used at the institution.

12.6.3 Informed Consent Process

The investigator or his/her authorized designee will inform the patient or the patient's legally authorized representative of all aspects pertaining to the patient's participation in the study.

The process for obtaining informed consent will be in accordance with all applicable regulatory requirements. The informed consent document must be signed and dated by the patient or the patient's legally authorized representative BEFORE the patient can participate in the study. In addition, the investigator will ensure that there is compliance with all institutional requirements for consent form execution. The patient will receive a copy of the consent and the original will be retained according to local requirements.

12.7 Protection of Patient Rights

12.7.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the patient's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the Informed Consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits. The IRB must give full board approval of the protocol and consent documents before the study may begin at a site.

12.7.2 Confidentiality of Patient Data

The clinical site is responsible for the confidentiality of the data associated with patients registered/randomized in this study in the same manner it is responsible for the confidentiality of any patient data within its sphere of responsibility. For patients registered/randomized to this study, there are additional considerations related to the necessity of sharing of research data with the ACOSOG-CC and representatives of NCI and OHRP.

The Privacy Rule (Title 45, Code of Federal Regulations, Parts 160 and 164) created as a result of the enactment of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) protects the privacy of individually identifiable health information. The rule's requirements also heighten the protection of patient information by introducing more controls on its use and disclosure. HIPAA refers to patient information as "protected health information" (PHI). PHI includes any information that could identify a person, living or dead. To comply with the HIPAA Privacy Rule, the patient is required to authorize the use and disclosure of his/her PHI by either signing a HIPAA-compliant informed consent document or a separate authorization form created for this purpose. The provisions of the Privacy Rule do not negate the other federal regulations that govern the protection of patient's rights relative to data confidentiality and the use of research data.

12.8 Inclusion of Women and Minorities

In conformance with the National Institute of Health *(NIH)* Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, *exploratory* comparisons will be conducted for pain reduction within gender and race, although our small sample size will preclude any definitive conclusions. Every effort will be made to include participants of all ethnicities and genders.

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	**1**	**1**	**2**
Not Hispanic or Latino	**26**	**27**	**53**
Ethnic Category: Total of all subjects*	**27**	**28**	**55**
Racial Category			
American Indian or Alaskan Native	**0**	**0**	**0**
Asian	**1**	**1**	**2**
Black or African American	**2**	**2**	**4**
Native Hawaiian or other Pacific Islander	**0**	**0**	**0**
White	**24**	**25**	**49**
Racial Category: Total of all subjects	**27**	**28**	**55**

12.9 Clinical Site Audits

All clinical sites at which patients are enrolled are subject to an audit by ACOSOG in accordance with guidelines provided by and available from the Clinical Trials Monitoring Branch (CTMB) of the NCI. Information on these regulations may be obtained from the CTMB web site at http://ctep.cancer.gov/.

12.10 Clinical Monitoring

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

13 Physician Skill Verification

Completed skills verification forms should be sent to the contact listed below:

Damian E. Dupuy, MD

Department of Diagnostic Imaging

593 Eddy Street

Providence, Rhode Island 02903

All treating physicians or treatment teams (if a radiologist and surgeon are both participating in the procedures) have performed 25 static or dynamic image guided thoracic procedures as well as 10 lung RFA ablation procedures with at least one with the Valley Lab system. If there are less than 10 RFA lung procedures then a minimum of 5 procedures and attendance at a CME approved course in RFA is required. All credentialing forms (Appendix 15.4) will be reviewed by the PI and Surgical Co-PI.

14 References

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15 Appendices

15.1 Abbreviations

ACOSOG	American College of Surgeons Oncology Group
ACRIN	American College of Radiology Imaging Network
AE	Adverse Event
CPA	Cooperative Project Assurance
CRF	Case Report Form
CTC	Common Toxicity Criteria
CTEP	Cancer Therapy Evaluation Program
CTMB	Clinical Trials Monitoring Branch
FDA	Food and Drug Administration
IDB	Investigational Drug Branch
IRB	Institutional Review Board
MPA	Multiple Project Assurance
NCI	National Cancer Institute
NIA	Non-institutional Investigator Agreement
NSCLC	Non-Small Cell Lung Cancer
OHRP	Office of Human Research Protection
OIR	Optical Image Recognition
RFA	Radio Frequency Ablation
RW	Registration Worksheet
SAE	Serious Adverse Event
SoF	Schedule of Forms
SOP	Standard Operating Procedures

15.2 Staging Reference

The staging criteria are adapted from: TNM Definitions (AJCC Cancer Staging Manual, 6th Edition, 2001).

Stage	Criteria
Primary tumor (T)	
TX	Primary tumor cannot be assessed, or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.
T0	No evidence of primary tumor.
TIS	Carcinoma in situ.
T1	Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (e.g., not in main bronchus). 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.
T2	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.
T3	Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium. 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.
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina, separate tumor nodule(s) in the same lobe, or tumor with a malignant pleural effusion. Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathological examinations of pleural are negative for tumor. In these cases, fluid is non-bloody and is not an exudate. 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.
Nodal Involvement (N)	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes involved by direct extension of the primary tumor.
N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s).
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s).
Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed.
M0	No distant metastasis.
M1	Distant metastasis present (includes synchronous separate nodule[s] in a different lobe).

Stage Grouping:

Stage	TNM
IA	T1, N0, M0
IB	T2, N0, M0
IIA	T1, N1, M0
IIB	T2, N1, M0; T3, N0, M0
IIIA	T1, N2, M0; T2, N2, M0; T3, N1, M0; T3, N2, M0
IIIB	Any T, N3, M0; T4, Any N, M0
IV	Any T, Any N, M1

15.3 ECOG/Zubrod Performance Status Scale

0	Asymptomatic and fully active.
1	Symptomatic; fully ambulatory; restricted in physical strenuous activity.
2	Symptomatic; ambulatory; capable of self-care; more than 50% of waking hours are spent out of bed.
3	Symptomatic; limited self-care; spends more than 50% of time in bed, but not bedridden.
4	Completely disabled; no self-care; 100% bedridden.

15.4 Physician Qualifications

Name of Institution: _____

RFA Treating Physician Information

RFA Treating Physician Name _____

Specialty: (Circle) Thoracic Surgery or Radiology

If thoracic surgeon, ACOSOG ID: _____

Signature: _____

Address: _____

Telephone: _____ Fax: _____

E-mail: _____

Research Associate's Name: _____

Thoracic Surgeon Information (if different from above)

Note: If RFA Treating Physician is a radiologist, an ACOSOG thoracic surgeon will evaluate all patients before recommending RFA. Please provide thoracic surgeon information below:

Thoracic Surgeon Name: _____

Signature: _____

ACOSOG ID: _____

Address of ACOSOG surgeon: _____

Telephone: _____ Fax: _____

Research Associate's Name: _____

Does your institution have a CT with helical/spiral capability? (Circle) Yes or No

If yes what brand and type: _____

Number of Image-Guided Thoracic procedures performed: _____ (25 required)

Number of Lung RFA procedures performed: _____ (10 required)

Number of Lung RFA done with Valley Lab device: _____ (1 required)

Outcome after lung RFA: _____

Number 30-day mortality: _____

If >0; Brief description: _____

Number of cases with bleeding requiring intervention: _____

If >0; Brief description: _____

Number of RFA procedures performed with Radionics Device: _____ (1 required)

If less than 10 RFA procedures, then 5 - 9 with attendance to a CME course on RFA (required).

Course name: _____

Physician in charge: _____

Location: _____

Dates (inclusive): _____

15.5 Model Consent Form for ACOSOG Study Z4033

A Pilot Study of Radiofrequency Ablation in High-Risk Cancer Patients with Stage IA Non-small Cell Lung Cancer

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 may have a small lung cancer. Your surgeon has determined that, if tests confirm that you do have lung cancer, attempting to remove it surgically would be a high-risk procedure, given your current health.

Why is this study being done?

The purpose of this study is to find out whether a procedure called *radiofrequency ablation* can help control the kind of lung cancer you may have.

Radiofrequency ablation is a procedure that uses radio waves to cause heating. This heat can kill cancer cells, as well as surrounding normal tissue, in a small area.

How many people will take part in the study?

About 55 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.

- The doctor will perform a physical exam.
- The doctor will ask you about your medical history.
- You will be given a PET scan and a CT scan (these are types of imaging that the doctor will use to examine your lung cancer).

During the study …

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body:

Radiofrequency Ablation Procedure - The Radiofrequency Ablation will be done at your hospital or clinic. It will be an outpatient procedure, meaning that you will not have to be hospitalized and are expected to be able to return home after the procedure.

- On the day of your radiofrequency treatment, an *Intravenous Tube* (a tube that goes into your vein) will be placed. You will be given sedation and medicines through this Intravenous Tube (also called an *IV*) to reduce any discomfort you might have during the procedure.
- You will need to lie still on your stomach or back for about one hour during the treatment.
- During the treatment, you will be placed in a *CT Scan Machine* (a type of X-ray machine that can take computerized images of the body).
- At the site of your cancer, your skin will be cleaned and draped to make the area sterile, to reduce the risk of infection.
- You will be given an injection of a medicine that will "numb" the area where the procedure will take place, in order to reduce discomfort.
- The doctor will use the images from the CT scan to help place a needle, which will be put directly into the lung cancer.
- This needle will be used as a guide while an electrode (an electrical device which will deliver the therapy) will be put into the lung cancer.
- Padding will be placed on your chest or back to "ground" you (this is process which helps keep you safe while electricity is being used).
- The electrode will be attached to a *radiofrequency generator*, a device that will produce the radio frequencies used to heat the cancer.
- Your lung cancer will then be treated with one radiofrequency heating for a period of time that could range from about 12 minutes to about 36 minutes (i.e. no other RFA will be given even if it appears there is tumor shrinkage).
- After the procedure is finished, you will need to stay in the hospital or clinic for about 4 hours. While you are in the hospital, the doctor and the staff will make sure that any pain you have is being treated, and that you are recovering safely from the medicine given to sedate you.
- When you have recovered from the sedation (this will take about 2 hours) you will be given a chest X-ray to check whether you have had any lung collapse. Lung collapse is a possible side effect of having this procedure. If it does happen, your doctor will give you treatment for it.

When I am finished with the procedure:

Within 24 to 96 hours of finishing the Radiofrequency Ablation procedure, you will be given a PET scan. This PET scan is being done as part of the research for this study and is not a part of the normal standard of care. This scan is required for the first 30 patients on this trial and is optional for the remaining patients. Your study doctor will let you know if you need to have this scan. If you need to have this scan, it will be paid for by the study. The information from this scan and your clinical information will be stored for potential future use in an archive at the National Cancer Institute (NCI) and the NCI's Cancer Imaging Program.

You will be asked to return to hospital or clinic for some follow-up procedures. You will be asked to return at 3, 6, 9, 12, 18, and 24 months after your procedure to be given a CT scan. At the 6, 12, 18, and 24-month visits, you will also be given a PET scan.

You will be asked to return at 24 months for repeat pulmonary function testing.

Study Chart

This chart is provided to make it easier for you to understand what procedures are being done, and when they are being done.

Radiofrequency Ablation Procedure

Before the radiofrequency ablation you will be sedated, medicated to cause drowsiness or complete sleep.

Day	What you do
Before starting the study procedure	• Get a physical exam • Provide your medical history to the doctor • Answer some questions that relate to how well you are breathing, whether you have shortness of breath, and how well you are feeling generally. • Pulmonary Function testing • Pregnancy testing
Day 1 (the day of your procedure)	• An IV tube will be placed • You will be given sedation • You will be placed in a CT Scan Machine • You will be given an injection to numb the area where your cancer is • You will have a needle placed in the area where your cancer is • The needle will be used to guide an electrode to the cancer, and the electrode will be used to heat the cancer • You will be taken to a recovery area where the doctor and the staff will make sure you are recovering from the procedure, and give you an X-ray.
Day 2-3	• Receive PET scan, if needed

Follow-Up Visits

Month	What you do
3 Months after procedure	• Get a CT scan and pulmonary function testing.
6 Months	• Get a CT scan and a PET scan.
9 Months	• Get a CT scan.
12 Months	• Get a CT scan and a PET scan.
18 Months	• Get a CT scan and a PET scan.
24 Months	• Get a CT scan, PET scan and pulmonary function testing.

How long will I be in the study?

Your participation in this study will begin when you sign this consent form. You will be given a physical examination and will be asked to answer some questions about your medical history and your health. You will be given a CT scan and a PET scan. Your doctor may also ask you to take other tests if he or she thinks it is necessary.

After these tests are completed, you will be given Radiofrequency Ablation treatment. This process will take about 2 hours.

Once you have completed the procedure, you will be asked to return to the hospital or clinic for a follow-up visit at 3, 6, 9, 12, 18, and 24 months after the procedure. At these visits, you will be given a physical examination, CT and/or PET scans, and asked to provide information about your current health, as well as any medical procedures or treatments you might have had since the last visit.

We would like to keep track of your medical condition for about 2 years. Your doctor may decide to take you off of this study before that time if:

- Your medical condition changes, or
- New information becomes available, which may affect whether you want to stay in this study.
- The study sponsor (ACOSOG) decides it must limit or stop the study.

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. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the procedure can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

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?

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 procedure has been finished. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the procedure include those that are:

Likely

- Pain at the injection site (you will be given medicine to numb the area being treated. You may also be given IV medicines to control the pain).
- Pain may be worsened with the procedure
- Weakness and numbness may happen if a nerve is near the area being treated.
- Infection (this procedure will cause some normal tissue to die. This may increase your risk of infection).

Less Likely

- Tissue damage from needle placement (the CT Scan will be used to minimize possible damage)
- Hemorrhage (bleeding) as a result of the RFA procedure, either during or after the operation
- A skin reaction at the site of injection
- Burn (second degree or greater) at the site of the electrode and grounding pads.
- Hemoptysis (a hemorrhage in your lungs as a result of the treatment. This may cause you to cough up blood).
- Empyema (a buildup of pus and fluid in the cavity around your lungs).

Rare but serious

- There is a risk of lung collapse during or after the procedure (if this happens, a small tube the size of a cocktail straw may be placed into your chest to remove the air. This tube may be left in place for up to 1-7 days depending on how well the collapsed lung can expand again, and how well the excess air between the lung and the chest wall can be removed).
- Respiratory failure
- Death

Reproductive risks: There are no known risks to becoming pregnant or fathering a child while on this study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope that this procedure will be more useful against cancer compared to the usual treatment (either no treatment or external beam radiation) there is no proof of this yet. We do know that the information from this study will help doctors learn more about Radiofrequency Ablation as a treatment for cancer. The radiofrequency device used in this protocol is approved for use in humans for the destruction of soft tissue lesions including, but not

limited to, lung lesions. However, the specific utility of radiofrequency ablation in the treatment of lung cancers that cannot be removed by surgery has not been studied prospectively. Therefore, its use in this application is the focus of this investigation and its potential benefit to you, or lack thereof, is not known.

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

Your other choices may include:

- Radiation therapy
- Chemotherapy
- No treatment, except for medication to make you feel better. This is known as comfort care or palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by cancer. It does not treat the cancer, 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.

When the American College of Surgeons Oncology Group (ACOSOG) gives researchers reports about your health, it will not give them your name, address, telephone number, or any information that could identify you.

Records of your study participation will be kept in confidential form at this institution and also in a computer file at the American College of Surgeons Oncology Group (ACOSOG) Coordinating Center. The confidentiality of the central computer record is carefully guarded. Your research records will include your medical history, the results of your exams, reports from your surgery and treatment, and reports of your office visits while on study. Some of the information collected as part of the research study may also be included in your medical records.

Also, your scan images and clinical information will be stored for potential future use in an archive at the National Cancer Institute (NCI) and the NCI's Cancer Imaging Program. No personal information will be included.

If the study results are published, no personal information will be identified. This is to ensure that no one will be able to tell that you took part in the study.

Organizations that may inspect and/or copy your research records in order to analyze data and ensure quality include groups such as:

- The American College of Surgeons Oncology Group (ACOSOG)
- Your local Institutional Review Board (IRB), a group of people at your hospital or clinic who review the research study and protect your rights
- Government agencies, including the Office of Human Research Protection (OHRP), the National Cancer Institute (NCI), the Food and Drug Administration (FDA), and other groups or organizations that have a role in the conduct of this research study.
- The American College of Radiology Imaging Network (ACRIN), which will receive copies of PET and CT scans.

However, no information by which you may be identified will be released or published.

What are the costs of taking part in this study?

Taking part in this study may lead to added costs you or your insurance company. Please ask about any expected added costs or insurance problems.

You or your insurance company will be charged for continuing medical care and or hospitalization.

You will receive no payment 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.]*

You will get a copy of all pages of this consent form and any new information gained during the study. You may also request a copy of the protocol (full study plan).

Signatures

I have read the consent form or it has been read to me. This information was explained to me and my questions have been answered to my satisfaction.

I voluntarily consent to be a subject in this research study and the procedures described in this consent form.

_____	_____
Date	Patient's Signature

16 Revision History

Date	Part	Description
01/17/2008	**Z4033 A3**	**ACOSOG activation**
01/16/2008	**Z4033 A3**	**NCI/CTEP approval**
Begin A3 changes:		
	Title page	**Updated:** Version number, NCI version date
	All pages	**Updated:** Footers
	Pg 2, Contacts	**Updated**: Contact names, numbers
	Pg 2, SOPs	**Deleted from SOP list:** DFQC Data Fax Quality Control
	Sec 2.1, pg 7, #3	**Added:** NOTE: If the evaluating surgeon is not a member of ACOSOG, then an ACOSOG thoracic surgeon must confirm with dated signature that the patient is high-risk and appropriate for RFA.
	Sec 2.1, pg 7, #4	**Changed from:** Patient must have FDG, PET, PFTs and a CT scan of the chest with upper abdomen within 60 days of prior to registration. **Changed to:** Patient must have FDG-PET and a CT scan of the chest with upper abdomen within 60 days prior to pre-registration. Patient must have PFTs within 120 days prior to registration.
	Sec 2.1, pg 7, #6 Major Criteria	**Changed from:** o FEV1% ≤ 50% o DLCO ≤ 50% **Changed to:** o FEV1 ≤ 50% predicted o DLCO ≤ 50% predicted
	Sec 2.2, pg 8, second bullet	**Parenthetical statement changed from:** (Exceptions: patients treated for basal cell carcinoma or carcinoma in situ of the cervix). **Parenthetical statement changed to:** (Exceptions: patients treated for non-melanoma skin carcinoma or in-situ carcinomas).
	Sec 3.0, pg 9, first column	**Added:** * footnote reference to CT and PET (see new * footnote below).
	Sec 3.0, pg 9, "Prior to patient registration" column	**Column title changed to: Prior to patient pre-registration** **Added:** footnote 1 reference to PFTs, CT, PET (see footnote 1 changes below)
	Sec 3.0, pg 9, "24 - 96 hours Post-RFA" column	**Added:** footnote 5 reference to PET (see new footnote 5 below)
	Sec 3.0, pg 9, Footnotes	**Added to end of footnote 1**: PFTs are required within 120 days of prior to the date of the pre-registration. **Added as new footnote 5**: The post-RFA 24-96 hour PET scan is for research purposes only. The scan may be a limited scan of the chest from neck to femora. If this PET scan is performed on a PET/CT scanner, it should be conducted without IV contrast. NOTE: Sites will receive reimbursement for this scan for the first 30 patients. 24-96 hour scans for subsequent patients will be optional. All sites will be notified within 24 hours when the first 30 patients have been accrued. **Added as new * footnote**: Follow-up CT and PET scans may be performed on the same day if a PET/CT scanner is used.
	Sec 4.1, pg 10	**First and second bullets changed from:** The ACOSOG ID number...

		First and second bullets changed to: The ACOSOG or CTEP ID number...
	Sec 4.2, pg 10, 3rd paragraph	**Deleted:** The site should fax the completed Registration Worksheet (RW) to the ACOSOG DataFax system at (919) 668-8466. Sites are encouraged to fax the RW within 24 hours of patient randomization, if possible. In the event that RW is not promptly received, sites will receive an automated e-mail reminder until receipt of the RW is confirmed.
	Sec 5.4.1 (new section), pg 12, Post-RFA PET Scan	**Added:** **5.4.1 Post-RFA PET Scan** **A post-intervention FDG-PET scan will be performed within 24-96 hours of completion of the RFA procedure**. The post-RFA 24-96 hour PET scan is for research purposes only. The scan may be a limited scan of the chest from neck to femora. If this PET scan is performed on a PET/CT scanner, it should be conducted without IV contrast. **Sites will receive reimbursement for this scan for the first 30 patients. 24-96 hour scans for subsequent patients will be optional. All sites will be notified within 24 hours when the first 30 patients have been accrued.**
	Sec 6, pg 12, Follow-up, 1st paragraph	**Changed from:** Protocol follow-up will be performed at 3, 6, 9, 12, 18, and 24 months. **Changed from:** Protocol follow-up will be performed at 3, 6, 9, 12, 18, and 24 months as required by the Study Calendar.
	Sec 6, pg 12, Follow-up, 2nd paragraph	**Changed from:** Patients will be monitored for local recurrence and distant recurrence and progression for two years. Patients also will be monitored for additional primaries and regional recurrence, with histological confirmation whenever possible. A CT scan will be performed 3, 6, 9, 12, 18 and 24 months. A PET scan will be performed pre-RFA and within 24-96 hours of completion of RFA procedure, and again at 6, 12, 18 and 24 months. The CT scan could also be performed on the same day if a PET/CT scanner is used. Pulmonary function tests (including DLCO) will be performed within 60 days pre-RFA and at 3 months and 24 months post RFA. **Changed to:** Patients will be monitored for local recurrence, regional recurrence and distant recurrence for two years as required by the Study Calendar. Patients also will be monitored for additional primaries, with histological confirmation whenever possible.
	Sec 7.1, pg 13, recurrence definitions	**Changed from:** **Distal Recurrence** Distal recurrence is indicated when a follow-up examination shows recurrence within a contralateral, mediastinal (N3) nodes or distant metastatic disease, visible on radiological images (nodule-enhanced Chest CT; see section 9.1). **Changed to:** **Distant Recurrence** Distant recurrence is indicated when a follow-up examination shows recurrence within a contralateral lobe, contralateral mediastinal (N3) nodes or distant metastatic disease, visible on radiological images (nodule-enhanced Chest CT; see section 9.1).
	Sec 9.2.5, pg 18, new 2nd and 3rd paragraphs	**Added:** NOTE: The post-RFA 24-96 hour PET scan is for research purposes only. The scan may be a limited scan of the chest from neck to femora. If this PET scan is performed on a PET/CT scanner, it should be conducted without IV contrast. **Sites will receive reimbursement for this scan for the first 30 patients. 24-96 hour scans for subsequent patients will be optional. All sites will be notified within 24 hours when the first 30 patients have been accrued.**
	Sec 10.0, pg 20, first paragraph	**Deleted from end of paragraph:** When printing CRF PDF files, make sure that the box labeled "Fit to Page" in the print dialog box is **NOT marked**. This will assure that the CRF is printed in its proper size.
	Sec 10.1, pg 20	**Deleted:** The CRF completion and submission guidelines are available on the ACOSOG web site with the DataFax CRFs. Institutions completing DataFax CRFs are required to read and follow the completion and submission guidelines. The CRF completion guidelines allow for maximum optical character recognition (OCR) within DataFax. ACOSOG studies require the submission of certain non-DataFax (non-barcoded) forms such as

		Pathology Reports and Operative Reports. For these forms, report-specific **Shuttle Forms** will be provided with the CRFs on the ACOSOG web site. **NOTE**: The CRF cannot be used in lieu of the patient's medical record. The CRF is used for transcription of source documentation FROM the preexisting medical record **only**. **Added:** This trial will utilize the Mayo Clinic Cancer Center Remote Data Capture system for data entry. You can access the system through the following URL https://ncctg.mayo.edu/acosog. Instructions on how to use this system are located on the web site under the header "instructions". The Clinical Research Associate who will be responsible for data entry will need to apply for a user ID and password prior to use. Please contact the Disease Site Coordinator for details.
	Sec 10.2, pg 20	**Deleted from first sentence:** DataFax
	Sec 12.1, pg 22, first paragraph	**First sentence changed from:** The investigator intending to register a patient to this study must... **First sentence changed to**: The investigator intending to register a patient to this study (radiologist or thoracic surgeon) must...
	Sec 12.1, pg 22	**Added to end of section: NOTE: The thoracic surgeon responsible for confirming the patient's appropriateness for RFA must be an ACOSOG member.**
	Sec 12.2, pg 22, first paragraph	**First sentence changed from:** All enrolling investigators... **First sentence changed to:** All enrolling and treating investigators...
	Sec 15.4, pg 30, Physician Qualifications	**This form has been clarified to request separate contact information for RFA Treating Physician and Thoracic Surgeon, if they are different.**
	Sec 15.5, pg 32, Model Consent, "When I am finished with the procedure"	**Added to end of first paragraph:** This scan is required for the first 30 patients on this trial and is optional for the remaining patients. Your study doctor will let you know if you need to have this scan. If you need to have this scan, it will be paid for by the study. The information from this scan and your clinical information will be stored for potential future use in an archive at the National Cancer Institute (NCI) and the NCI's Cancer Imaging Program.
	Sec 15.5, pg 36, "Will my medical information be kept private?"	**Added as new third paragraph:** Also, your scan images and clinical information will be stored for potential future use in an archive at the National Cancer Institute (NCI) and the NCI's Cancer Imaging Program. No personal information will be included.
	Sec 15.5, pg 38, end of form	**Deleted:** Signature of Person Obtaining Consent
End of A3 changes		
08/22/06	**Page 1**	**Updated:** Version title , date, headers and footers
	Page 2	**Updated:** Contact Information
	Page 2	**Deleted:** SpecBank, ACOSOG Central Specimen Bank
	Page 5	**Changed From**: 22 **Changed To**: 24
	Page 5	**Updated:** Dupuy 2006 reference
	Page 5	**Added:** Vansteenkiste 2004 reference
	Page 5	**Updated:** ACS 2003 estimate of 171,900 to 2005 estimate of 163,510 and references
	Page 5	**Updated:** References 2005 [ACS 2005] & [ACS 2005].
	Page 6	**Deleted:** and Quality of Life (QOL
	Page 6	**Deleted:** at 2 years
	Page 6	**Added:** Current external beam radiotheraphy data in this groups of patients has reported a 2 year survival of 51% [Bradley 2003].
	Page 6	**Deleted:** and QOL
	Page 6	**Changed From**: To assess the survival rate at 2-years for sites deemed qualified by expert review **Changed To**: To assess the overall 2 year survival rate after RFA.
	Page 6	**Changed From**: To assess freedom from local recurrence in the ablated lobe at 2 years. To estimate the number of procedures deemed technical successes.

		To evaluate procedure-specific morbidity and mortality. To explore the impact of imaging features of RFA on overall survival and local control. To explore the utility of immediate (within 96 hours) post RFA PET in predicting overall survival and local control. To explore the effect of RFA on both short term (3 months post RFA) and long term (24 months post RFA) pulmonary function. Definition for local control: no recurrence in the same lobe or hilum (N1 nodes) or progression at the ablated site after treatment affects have subsided. Definition for technical success: The pertinent captured images from the treatment CT showing RFA electrode placement and the recorded RFA generator parameters (e.g. impedance, current, power, treatment time and maximum intra-tumoral temperature) will be reviewed by the quality control panel to determine technical success. **Changed To**: To assess freedom from regional or distant recurrence. *Definition for regional recurrence: recurrence within another lobe on the same side of ablation, or the ipsilateral mediastinal or subcarinal (N2) nodes.* *Definition of distant recurrence: contralateral, mediastinal (N3) nodes or distant metastatic disease.* To assess freedom from local recurrence in the ablated lobe at 2 years. *Definition for local recurrence: no recurrence in the same lobe or hilum (N1 nodes) or progression at the ablated site after treatment affects have subsided*. To estimate the number of procedures deemed technical successes. *Definition for technical success: The pertinent captured images from the treatment CT showing RFA electrode placement and the recorded RFA generator parameters (e.g. impedance, current, power, treatment time and maximum intra-tumoral temperature) will be reviewed by the quality control panel to determine technical success*. To evaluate procedure-specific morbidity and mortality. To explore the utility of immediate (within 96 hours) post RFA PET in predicting overall survival and local control. To explore the effect of RFA on both short term (3 months post RFA) and long term (24 months post RFA) pulmonary function.
	Page 6	**Changed From:** 20 **Changed To:** 22
	Page 7	**Deleted:** or selected Ib (i.e., with visceral pleural involvement).
	Page 7	**Added:** FDG, PET, PFTs and
	Page 8	**Added:** within 2 weeks of registration
	Page 8	**Deleted Performance Monitoring:** Up to 20 sites will be allowed to initially enroll up to 2 patients. When a site enrolls their first patient, the RFA images and data for the patient will be reviewed by an expert panel. If the procedure is rated successful, the site can enroll their second patient. Again, the RFA images and data will be reviewed for this patient by the expert panel. If both patient procedures are determined to be technical successes, the site will be deemed "qualified" for this trial. If the second procedure was deemed unsuccessful, the expert panel will determine whether the site is qualified based on the nature of the failure. If the procedure for the first patient is rated unsuccessful, feedback will be provided to the site for the purposes of technically improvement of the procedure prior to the enrollment of the second patient. If the second patient procedure is rated successful, the site will be deemed "qualified" for this trial. If the first patient procedure was rated unsuccessful and the second patient procedure also rated unsuccessful even after feedback received for technically improvement for performing the procedure, the site will be deemed "unqualified" for this study and not allowed to enroll any more patients. The first two patients of any "qualified" site will be used in evaluation of efficacy endpoint, the proportion of patients alive at two years. ***Note:*** *After sites have been deemed "qualified", they will be allowed to continue to enroll patients. SHOULD THERE BE A CAP OF A TOTAL OF 5 PATIENTS PER SITE? This will be challenging to implement. If a site does not qualify, they will not be allowed to enroll any more patients.* **Note**: Removed section 2.3 Performance Monitoring because this information is addressed in section 10.3.2 Quality Control oof RFA and Images.

	Page 8	**Deleted:** CT of abdomen to include liver and adrenal glands, as clinically indicated. In the event that liver and adrenal glands are imaged, radiographic reading of the CT MUST include comment about the presence or absence of lesions suspicious for metastatic disease in the liver and adrenals.
	Page 9	**Updated;** Study Calendar
	Page 11	**Deleted:** Patients are then brought to the CT scanner, where technical staff will place four grounding pads (in the horizontal configuration *1800cc^3/each)* on the opposite chest wall from the skin entry site (e.g. anterior chest wall for patient lying prone), in order to direct the RF current and thus prevent damage to adjacent structures in the target area. After the initial scout images are taken, a skin mark is placed on the patient corresponding to the skin entry site, as determined by the computer grid at the appropriate table position. Horizontal and vertical laser lights in the CT gantry correspond to the x- and y-axes from the computer grid on the screen, and a ruler may be placed to match the desired skin entry site as determined on the computer screen.
	Page 11	**Deleted:** The area is prepped and draped in sterile fashion and local buffered lidocaine anesthesia is administered both intradermally and to the level of the pleura with a 25-gauge skin needle and 22-gauge spinal needle, respectively.
	Page 11	**Changed From:** [Radionics Inc, Burlington, MA] **Changed To:** [Valley Lab, Boulder, CO]
	Page 11	**Added: Note**: CT images of the treatment electrode placement within the target lesion must be obtained prior to each activation of the RF generator. These images should also be among the images transferred to ACRIN and archived. These images are necessary to ascertain the technical success and quality of treatment
	Page 12	**Deleted:** and QOL using the SF-36 and UCSD Shortness of Breath Questionnaire
	Page 12	**Changed From:** Pulmonary function tests (including DLCO) will be performed pre-RFA and at 3, 6, 12 and 24 months. **Changed To:** Pulmonary function tests (including DLCO) will be performed within 60 days pre-RFA and at 3 months and 24 months post RFA.
	Page 12-13	**Changed From:** Local recurrence is indicated when a follow-up examination shows growth of primary tumor or abnormality in the treated lobe visible on radiological images (nodule-enhanced Chest CT and PET; see sections 9.1 and 9.2). Since scarring may occur adjacent to the ablation site, a CT scan will be obtained at 3 months. This will form the baseline study against which local recurrence will be judged. **Changed To:** **Local Recurrence** Local recurrence is indicated when a follow-up examination shows recurrence in the same lobe or hilum (N1 nodes) or progression at the ablated site (local progression), visible on radiological images (nodule-enhanced Chest CT; see section 9.1) after treatment effects have subsided. Since scarring may occur adjacent to the ablation site, a CT scan will be obtained at 3 months. This will form the baseline study against which local recurrence will be judged. **Regional Recurrence** Regional recurrence is indicated when a follow-up examination shows recurrence within another lobe on the same side of ablation, or the ipsilateral mediastinal or subcarinal (N2) nodes, visible on radiological images (nodule-enhanced Chest CT; see section 9.1. **Distal Recurrence** Distal recurrence is indicated when a follow-up examination shows recurrence within a contralateral, mediastinal (N3) nodes or distant metastic disease, visible on radiological images (nodule-enhanced Chest CT; see section 9.1).
	Page 13	**Changed From:** Pulmonary function tests with diffusion capacity will be obtained after pre-registration and before full registration and at 3 and 24 months after the RFA procedure. **Changed To**: Pulmonary function tests with diffusion capacity will be obtained before pre-registration and at 3 and 24 months after the RFA procedure.
	Page 14	**Added:** Events (grade 3-5) related to the radiofrequency ablation procedure will be reported to 24 months on the AE CRF.
	Page 14	**Deleted:** All grade 3-5 long-term (> 30 days following the study intervention to the completion of the 24 months); expected and unexpected AEs **related to the Radiofrequency Ablation (RFA)** will be reported using the Adverse Event CRF (AE CRF)

	Page 15-16	**Added: Note**: CT images of the treatment electrode placement within the target lesion must be obtained prior to each activation of the RF generator. These images should also be among the images transferred to ACRIN and archived. These images are necessary to ascertain the technical success and quality of treatment
	Page 16	**Added:** or equivalent
	Page 16	**Deleted:** 3. Filming/print with standard soft tissue window: +400 HUwidth and +40 HU level; standard lung window: +1600 HU width and -550 HU level; Format: 20:1. DICOM data to be stored on CD (can be read at single or multiple sites).
	Page 17	**Added:** or equivalent
	Page 17	**Deleted:** 3**.** Filming/print: Standard soft tissue window: +400 HU width and +40 HU level. Standard lung window: +1600 HU width and -550 HU level. Format: 20:1 DICOM data to be stored on CD (can be read at single or multiple sites).
	Page 17	**Added:** (as determined on lung windows)
	Page 17	**Changed From:** CT-guided fine needle aspiration biopsies will be performed for all patients with changes in the treated nodule that are suspicious for recurrence. **Changed To:** CT-guided fine needle aspiration biopsies will be performed when clinically appropriate for all patients with changes in the treated nodule suspicious for recurrence.
	Page 19	**Added:** when clinically appropriate.
	Page 19	**Added: Note**: For digital images the full set of digital image data will be considered acceptable and that while processed images such as jpeg format images, may be provided they will not be considered sufficient or compliant with this protocol.
	Page 19	**Deleted:** Plain film images may be sent via mail for digitization and subsequent entry to the image archive, if applicable.
	Page 19	**Deleted:** and film
	Page 19	**Deleted:** screened-film images or
	Page 20	**Deleted:** This will allow deviations from protocol to be detected at the earliest possible time
	Page 20	**Added:** These necessary and important images are critical to ascertain the technical success and quality of treatment and will also be used to qualify sites and monitor quality.
	Page 20	**Changed:** Entire Section, Quality Control of Procedures and Images **Changed To:** Section, Quality Control of RFA and Images Quality Control will be established to monitor the protocol compliance with the RFA procedure. The first 20 sites that are eligible (regulatory submission complete, IRB approval, contract executed, etc.) will be allowed to initially enroll 2 patients each. The Study Chair and Study Co-Chair, will review after each enrollment, the pertinent images from the treatment CT showing the RFA electrode placement and the RFA generator parameters (e.g. impedance, current, power, treatment time and maximum intra-tumoral temperature). In addition, the contrast CT studies will be analyzed by a panel of 2 individuals from the protocol team including a radiologist with thoracic imaging expertise for an additional 5 quality control measures: adequacy of contrast administration, proper field of view, collimation, appropriate tumoral coverage and lack of patient motion. Technical successes and failures will be recorded and any deviations will be communicated to the site investigator by the Study Chair. If both cases are deemed technical successes the site will be deemed qualified and may continue to enroll patients. If one procedure is a technical success and the other is a technical failure the expert panel will determine whether the site is qualified based on the nature of the failure. A total of 2 technical failures from any one site will result in termination of enrollment privileges.
	Page 21	**Changed:** Entire Section, Statistical Considerations
	Page 22	**Added:** Without prejudices the ACOSOG will facilitate membership for surgeons/radiologist's

		who are interested in being a PI on this study.
	Page 26	**Changed From:** All treating physicians are required to have performed 25 lung procedures as well as 10 RFA ablation procedures including one with the Radionics RFA system. Physicians performing the RFA procedure for the trial will need to complete a skills verification form prior to participation (appendix 16.5). **Changed To:** All treating physicians or treatment teams (if a radiologist and surgeon are both participating in the procedures) have performed 25 static or dynamic image guided thoracic procedures as well as 10 lung RFA ablation procedures with at least one with the Valley Lab system. If there are less than 10 RFA lung procedures then a minimum of 5 procedures and attendance at a CME approved course in RFA is required. All credentialing forms (Appendix 15.4) will be reviewed by the PI and Surgical Co-PI.
	Page 27	**Updated References**
	Page 31	**Updated Physicians Qualifications Form**
	Page 34	**Deleted:** ***Questionnaires*** You will be asked to fill out several questionnaires. These will contain questions relating how well you can breathe, or any problems you may have had with breathing. Another questionnaire will contain questions about your general health and well-being. You will be given these questionnaires before you have the Radiofrequency Ablation Treatment, and again after your treatment is completed at intervals of 3, 6, 12, and 24 months.
	Page 34	**Deleted:** At the 3, 6, 12, and 24-month visits, you will be asked to fill out questionnaires about how well you can breathe, or any difficulty you may have had breathing, as well as a questionnaire about your general health and well-being.
	Page 34	**Added:** You will be asked to return at 24 months for repeat pulmonary function testing.
	Page 34	**Deleted:** Quality of life references in Follow-up Visits table
	Page 34	**Added:** and pulmonary function testing to Follow-up Visits table
	Page 35	**Deleted:** You will be asked to answer some questionnaires about how well you can breathe, as well as how well you are feeling in general.
	Page 37	**Changed From**: Radiofrequency Ablation is a standard technique used for liver tumors, but is experimental technique with lung cancer. This information could help future cancer patients. **Changed To:** The radiofrequency device used in this protocol is approved for use in humans for the destruction of soft tissue lesions including, but not limited to, lung lesions. However, the specific utility of radiofrequency ablation in the treatment of lung cancers that cannot be removed by surgery has not been studied prospectively. Therefore, its use in this application is the focus of this investigation and its potential benefit to you, or lack thereof, is not known.
07/11/2006	**Page 1**	**NCI-CTEP Submission**
07/11/2006	**Page 1**	**Version Title and Date**
07/11/2006	**Page 2**	**Updated:** Contact information
07/11/2006	**Page 6**	**Changed From:** A monthly accrual of 5 patients is expected, (with an expected start-up time of 3 to 6 months, and the reality that some patients may not qualify the projected enrollment goal has been extended to 20 months verses 11) with a resulting projected time line of 20 months to reach the total accrual goal. **Changed To**: We estimate that 5 patients per month will be enrolled and conservatively 2-3 of these 5 patients will come from sites that are later deemed "qualified" with a projected enrollment period of 20 months.
07/11/2006	**Page 10**	**Added:** Pregnancy test to Study Calendar
07/11/2006	**Page 23**	**Changed From:** Most institutions have Multiple Project Assurance (MPA), Cooperative Project Assurance (CPA) number or Federal Wide Assurance (FWA)… **Changed To:** An ACOSOG member must enroll patients at clinical sites (institutions) that have a valid Federal Wide Assurance (FWA) number from the United States Office for Human Research Protections (OHRP).
07/11/2006	**Page 37**	**Added:** Before the radiofrequency ablation you will be sedated, medicated to cause drowsiness or complete sleep.
07/11/2006	**Page 37**	**Added:** Pulmonary Function testing & Pregnancy testing
07/11/2006	**Page 38**	**Deleted:** Schema…already addressed, redundant
07/11/2006	**Page 40**	**Added**: Radiofrequency Ablation is a standard technique used for liver tumors, but is

		experimental technique with lung cancer.
07/11/2006	**Page 43**	**ADDED**: You will get a copy of all pages of this form. You may also request a copy of the protocol (full study plan). **Signatures** I have read the consent form or it has been read to me. This information was explained to me and my questions have been answered to my satisfaction. I voluntarily consent to be a subject in this research study and the procedures described in this consent form.
04/28/2006	**Z4033**	**NCI-CTEP Submission**
04/28/2006	**Title page**	**NCI Version Date** Updated
04/28/2006	**Page 2**	**ACOSOG Contact Information table:** Updated
04/28/2006	**Page 2**	**ACOSOG SOPs**: Deleted DFQC, Drugs & SpecBank from SOPs, not needed.
04/28/2006	**Page 5**	**Background:** Added reference Vansteenkiste 2004.
04/28/2006	**Page 5**	**Rational:** Changed reference & number 2003 number 171,900 to 2005 number 163,510.
04/28/2006	**Page 5**	**Rational:** Updated statistical references from 2003 to 2005.
04/28/2006	**Page 6**	**Rational:** Deleted reference to QOL
04/28/2006	**Page 6**	**Primary Objectives**: **Changed From:** To define technical guidelines and establish quality assurance methodology for Radiofrequency Ablation (RFA) of lung nodules. To assess freedom from local recurrence in the ablated lobe at 2 years. (Local recurrence includes recurrence within the same lobe or hilum (N1 nodes) or progression at the ablated site after treatment effects have subsided). **Changed to:** To assess the survival rate at 2-years for sites deemed qualified by expert review.
04/28/2006	**Page 6**	**Secondary Objectives**: **Changed From**: To establish procedure-specific morbidity and mortality. To analyze the imaging features of RFA and determine how they may relate to the treatment effects. To prospectively explore the utility of immediate (within 48 hours) post-RFA PET scan in establishing correlations with long-term outcomes. To determine the effect of RFA on pulmonary function. To determine the effect of RFA on patient Quality of Life. **Changed To:** To assess freedom from local recurrence in the ablated lobe at 2 years. To estimate the number of procedures deemed technical successes. To evaluate procedure-specific morbidity and mortality. To explore the impact of imaging features of RFA on overall survival and local control. To explore the utility of immediate (within 96 hours) post RFA PET in predicting overall survival and local control. To explore the effect of RFA on both short term (3 months post RFA) and long term (24 months post RFA) pulmonary function.

		Definition for local control: no recurrence in the same lobe or hilum (N1 nodes) or progression at the ablated site after treatment affects have subsided. Definition for technical success: The pertinent captured images from the treatment CT showing RFA electrode placement and the recorded RFA generator parameters (e.g. impedance, current, power, treatment time and maximum intra-tumoral temperature) will be reviewed by the quality control panel to determine technical success.
04/28/2006	**Page 6**	**Study Design and Accrual**: **Changed From:** This study consists of a single arm pilot trial. The study will accrue 55 patients with the anticipation that 53 patients will be eligible. A monthly accrual of 5 eligible patients is expected, with a resulting projected time of 20 months to reach the total accrual goal. **Changed To:** This study consists of a single arm pilot trial. The study will accrue 55 patients from sites deemed qualified by expert review. A monthly accrual of 5 eligible patients is expected, (with an expected site start-up time of 3 to 6 months, and the reality that some patients may not qualify the projected enrollment goal has been extended to 20 months verses 11) with a resulting projected time of 20 months to reach the total accrual goal.
04/28/2006	**Page 9**	**Schema:** Changed "within 48 hours" to within 96 hours
04/28/2006	**Page 8**	**Eligibility Criteria:** Criteria # 2 **Changed From:** "Patient must have a mass ≤ 3 cm maximum diameter by CT size estimate: clinical stage Ia or selected Ib (i.e., with visceral pleural involvement)." **Changed To**: Patient must have a mass ≤ 3 cm maximum diameter by CT size estimate: clinical stage Ia.
04/28/2006	**Page 8**	**Eligibility Criteria:** **Deleted Pre-registration 9 and 10, redundant:** 9. Patient, or the patient's legally acceptable representative, must provide a signed and dated written informed consent PRIOR to registration and any study-related procedures being performed. 10. Patient or the patient's legally acceptable representative must provide written authorization to allow the use and disclosure of their protected health information. NOTE: This may be obtained in either the study-specific informed consent or in a separate authorization form and must be obtained from the patient PRIOR to registration and any study-related procedures being performed.
04/28/2006	**Page 8**	**Performance Monitoring:** **Added:** The first 20 sites that are eligible (regulatory complete, IRB approval, contract executed, etc.) to enroll subjects will be allowed to initially enroll up to 2 patients. When a site enrolls their first two patients, the RFA images and data for the patients will be reviewed by an expert panel. If the procedures are rated successful, the site can begin to enroll other patients. If the procedures are rated unsuccessful, the site will not be allowed to enroll any additional patients. If one procedure is a technical success and the other is not the expert panel will determine whether the site is qualified based on the nature of the failure and feedback will be given for technical improvement. The first 2 patients of any "qualified" site will be used in evaluation of all efficacy endpoints.
04/28/2006	**Page 9**	**Study Calendar**: **Added:** 24 – 96 hours Post RFA.
04/28/2006	**Page 9**	**Study Calendar**: **Deleted:** QOL (SF-36)
04/28/2006	**Page 9**	**Study Calendar**:

		Deleted: UCSD Shortness of Breath Questionnaire
04/28/2006	**Page 9**	**Study Calendar**: **Deleted:** 12 month Pulmonary Function follow-up
04/28/2006	**Page 9**	**Study Calendar**: Deleted "[2]CT of abdomen to include liver and adrenal glands, as clinically indicated. In the event that liver and adrenal glands are imaged, radiographic reading of the CT MUST include comment about the presence or absence of lesions suspicious for metastatic disease in the liver and adrenals" not auditable."
04/28/2006	**Page 11**	**Preparation:** **Deleted:** To reduce potential complications of sedation-induced nausea and aspiration of gastric contents, all patients are treated after an overnight fast. Patients on extensive medications, in particular hypertension and cardiac medications, may take these medications in the morning with a small quantity of water. Insulin dependent diabetic patients should administer half of their usual morning insulin dose. An abridged physical is performed outside the procedure suite and an intravenous line is placed. Thirty minutes prior to and after the commencement of the procedure all patients are given intravenous conscious sedation (fentanyl, versed, etc.) Droperidol can be used for its sedative and anti-emetic effects (Parkinson's patients should not receive droperidol as this may exacerbate their symptoms).
04/28/2006	**Page 11**	**Preparation:** **Deleted:** "on the opposite chest wall from the skin entry site (e.g. anterior chest wall for patient lying prone), in order to direct the RF current and thus prevent damage to adjacent structures in the target area."
04/28/2006	**Page 11**	**Preparation:** **Changed From:** "the area is prepped and draped in sterile fashion and local buffered lidocaine anesthesia is administered both intradermally and to the level of the pleura with a 25-gauge skin needle and 22-gauge spinal needle, respectively. CT-guidance is initiated and an image is taken with the spinal needle in place to identify proper table position and needle angle. Repositioning can be performed with the spinal needle if necessary. A small skin incision is made at the correct skin entry site by plunging a #11 scalpel blade 1-2 cm into the subcutaneous tissues. **Changed To:** "CT-guidance is initiated and an image is taken with the spinal needle in place to identify proper table position and needle angle. Repositioning can be performed with the spinal needle if necessary. A small skin incision is made at the correct skin entry site by plunging a #11 scalpel blade 1-2 cm into the subcutaneous tissues.
04/28/2006	**Page 11**	**Preparation:** **Changed From:** Radionics Inc, Burlington, MA **Changed To:** Valley Lab, Boulder CO.
04/28/2006	**Page 12**	**Electrode Removal and Post-intervention Evaluation and Treatment:** **Changed From:** "A post-intervention FDG-PET scan will be performed within 24-48 hours of completion of the RFA procedure" **Changed To:** 24 -96 hours.
04/28/2006	**Page 12**	**Follow-up:** **Changed From:** "the CT scan could also be performed on the same day if a PET/CT scanner is used. Pulmonary function tests (including DLCO) and QOL using the SF-36 and UCSD Shortness of Breath

		Questionnaire will be performed pre-RFA and at 3, 6, 12 and 24 months" **Changed To:** the CT scan could also be performed on the same day if a PET/CT scanner is used. Pulmonary function tests (including DLCO) will be performed pre-RFA and at 3 months and 24 months post RFA.
04/28/2006	**Page 12**	**Follow-up:** **Changed From:** "A PET scan will be performed pre-RFA and within 24-48 hours of completion of RFA procedure, and again at 6, 12, 18 and 24 months" **Changed To:** 24 – 96 hours.
04/28/2006	**Page 12**	**Evaluation of Outcomes:** **Changed From**: Local recurrence is indicated when a follow-up examination shows growth of primary tumor or abnormality in the treated lobe visible on radiological images (nodule-enhanced Chest CT and PET; see sections 9.1 and 9.2). Since scarring may occur adjacent to the ablation site, a CT scan will be obtained at 3 months. This will form the baseline study against which local recurrence will be judged". **Changed To:** Local recurrence is indicated when a follow-up examination shows recurrence in the same lobe or hilum (N1 nodes) or progression at the ablated site (local progression), visible on radiological images (nodule-enhanced Chest CT; see section 9.1) after treatment effects have subsided. Since scarring may occur adjacent to the ablation site, a CT scan will be obtained at 3 months. This will form the baseline study against which local recurrence will be judged. Regional Recurrence Regional recurrence is indicated when a follow-up examination shows recurrence within another lobe on the same side of ablation, or the ipsilateral mediastinal or subcarinal (N2) nodes, visible on radiological images (nodule-enhanced Chest CT; see section 9.1) after treatment effects have subsided. Distal Recurrence Distal recurrence is indicated when a follow-up examination shows recurrence within a contralateral, mediastinal (N3) nodes or distant metastic disease, visible on radiological images (nodule-enhanced Chest CT; see section 9.1) after treatment effects have subsided."
04/28/2006	**Page 13**	**Pulmonary Function Tests:** **Changed From:** "Pulmonary function tests with diffusion capacity will be obtained after pre-registration and before full registration and at 3, 6, 12 and 24 months after the RFA procedure" **Changed To:** 3 and 24 months.
04/28/2006	**Page 13**	**Quality of Life questionnaire and QOL attachment** **Delete:** "The patient population for this study is expected to exhibit significant pulmonary morbidity. As a secondary outcome, patient-centered QOL data will be measured using the SF36 and dyspnea will be measured using the UCSD Shortness of Breath Questionnaire [Eakin, 1998]. Each patient will serve as his or her own control. It will be important to quantify any changes in overall health and pulmonary-specific symptoms in this population. These validated instruments have been used in many trials of patients with severe lung disease. Measurements will be undertaken using the QOL instruments prior to intervention and again at 3, 6, 12 and 24 months after RFA procedure. QOL instruments will be completed by the patient at the time of a scheduled follow-up visit. In the event that the patient misses a follow-up visit, the patient will be able to fill out the QOL instrument and mail it to the physician."

04/28/2006	**Page 17**	**Quantitative Measurements:** **Changed From:** "any growth of the target lesion 1.25 times any dimension obtained at the 3 month baseline CT scan will be considered suspicious for recurrence and require biopsy. (If contrast enhancement performed: Any mass lesion measuring greater than 9mm in the treatment field that enhances 15HU within 1 minute after contrast injection will also be considered suspicious for recurrence.)" **Changed To:** CT-guided fine needle aspiration biopsies will be performed for all patients with changes in the treated nodule that are suspicious for recurrence. To Any growth of the target lesion 1.25 times any dimension obtained at the 3 month baseline CT (as determined on lung windows) scan or on subsequent CT scans will be considered suspicious for recurrence and require biopsy. (If contrast enhancement performed: Any mass lesion measuring greater than 9mm in the treatment field that enhances 15HU within 1 minute after contrast injection will also be considered suspicious for recurrence.) The results of the CT and biopsy will be used to assess the secondary endpoints.
04/28/2006	**Page 16**	**Imaging:** **Changed From:** "PET scan prior to patient registration, within 24-48 hours following completion of RFA procedure, and at 6, 12, 18, and 24 months post-RFA" **Changed To:** 24 – 96 hours.
04/28/2006	**Page 17**	**Pet Imaging Equipment:** **Added:** "it is strongly encouraged that all of the serial PET studies for this trial be done at the same institution and on the same scanner (or same type of scanner), using the same dose, imaging times and reconstruction parameters."
04/28/2006	**Page 18**	**FDG PET Imaging Parameters:** **Changed From:** "emission imaging will be started approximately 45-60 minutes after FDG injection" **Changed To:** 50-70 minutes.
04/28/2006	**Page 18**	**FDG PET Imaging Parameters:** **Deleted:** "When using hybrid PET/CT scanners, an attenuation CT scan with or without intravenous contrast agent administration should be acquired following the manufacturer's suggested parameters. The scan should be acquired at mid-inspiration or mid-expiration to minimize any misregistration artifacts between the PET and CT scans. A typical scan utilizing the GEMS Discovery ST system would require a helical scan, 13.5 mm/rotation, 80 mA 140 kV at 3.75 mm slice thickness. Each institution could acquire a diagnostic contrast enhanced scan utilizing current imaging protocols outlined in section 9.2. Standard CT reconstruction for soft tissue and bone/lung algorithms will be utilized to improve image correlation with PET.
04/28/2006	**Page 18**	**FDG PET Imaging Parameters:** **Changed From:** "PET image reconstruction will be done using manufacturer provided algorithms. For dedicated PET scanners we recommend an iterative reconstruction method with preference for OSEM reconstruction, 8 subsets, 2 iterations, followed by smoothing with a 6-mm 3D Gaussian kernel. For PET/CT units image reconstruction should be done using vendor provided reconstruction algorithms utilizing the CT dataset, and utilization of OSEM reconstruction is recommended".

		Changed To: PET image reconstruction will be done using manufacturer provided algorithms. For PET/CT unit's image reconstruction should be done using vendor provided reconstruction algorithms utilizing the CT dataset, and utilization of OSEM reconstruction is recommended.
04/28/2006	**Page 18**	**Image interpretation and analysis:** **Changed From:** "Interpretation will be both with qualitative and semiquantitative (determination of the peak standardized uptake value [SUV-peak] utilizing vendor-provided software). The SUV will be corrected utilizing body weight. No films will be utilized for image interpretation as the film exposure settings may affect visual interpretation. Lesions that are metabolically active and >1.5 cm in largest diameter should have a maximum SUV of greater than 2.5 to be considered as tumor. The nuclear medicine physician should visually identify 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 the CT scan. A circular region of interest 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 region; this value will be reported as the SUV-peak. If two or more regions of interest are analyzed, the one with the higher SUV-peak will be reported for the purposes of this protocol. **Changed To:** " Interpretation will be qualitative guided by semiquantitative results (determination of the maximum standardized uptake value [SUV-max] utilizing vendor-provided software). The SUV will be normalized to body weight. No films will be utilized for image interpretation as the film exposure settings may affect visual interpretation. In general, lesions that are metabolically active and >1.5 cm in largest diameter should have a maximum SUV of greater than 2.5 to be considered as tumor. The nuclear medicine physician should visually identify 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 the CT scan. A two-dimensional or three-dimensional region of interest centered on the maximum-value pixel will be drawn, and the manufacturer's algorithm will be used to calculate the maximum SUV within this region; this value will be reported as the SUV-max. If two or more regions of interest are analyzed, the one with the higher SUV-max will be reported for the purposes of this protocol. In addition, on post-RFA PET scans, a separate measurement of the SUV-max of the rim of increased activity surrounding the ablation site should be performed, if a visible rim is seen on the images."
04/28/2006	**Page 18**	**Post-RFA PET scans:** **Changed From:** "The post-treatment PET scan is to be done according to the same specifications described in detail above (Section 9.4.2). 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 ACOSOG/ACRIN-qualified institution used for the pre-treatment PET. A post-treatment PET scan will be done 24-48 hours following completion of **RFA**, and again at 6, 12, 18, and 24 months after the completion of **RFA**. Response assessment utilizing both the CT and PET data will be done. For qualitative assessment of the PET images, response criteria similar to those previously described by MacManus, et al. will be used [MacManus MP, Hicks RJ, Matthews JP, et al. 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*. 21: 1285-92, 2003]. Visual assessment of response will be used, as follows: • **Complete metabolic response:** No evidence of FDG uptake in the tumor or activity similar to that in the mediastinum • **Partial metabolic response:** Appreciable reduction in the intensity of tumor FDG uptake or tumor volume apparent to the nuclear medicine physician when pre- and post-treatment PET scan are compared, with no evidence of disease progression • **No metabolic response:** No appreciable reduction in the intensity of tumor FDG uptake or tumor volume apparent to the nuclear medicine physician when pre-and post-treatment PET scans are compared, with no evidence of disease progression • **Progressivemetabolic disease:** Appreciable increase in the intensity of tumor FDG uptake or tumor volume apparent to the nuclear medicine physician when pre- and post-treatment PET are compared or with evidence of disease progression at other sites For the semiquantitative analysis, a complete metabolic response is defined as resolution of

		abnormal FDG uptake (SUV-peak <2.5 in lesion area >1.5 cm). Partial metabolic response is defined as a greater than 20% decrease in SUV-peak from the baseline scan or significant decrease in size of lesion that is still metabolically active. Stable metabolically active disease is defined as an SUV-peak decrease less than 20% but no increase greater than 20%. Progressive metabolically active disease is defined as identification of new lesions, increase in lesion size, or interval increase in SUV.>20%. The interpretation of the scans will be done with full knowledge of the CT findings on dedicated scanners and with the accompanying CT for PET/CT as this improves the accuracy of the interpretation of the PET study. **Changed To:** "The post-treatment PET scan is to be done according to the same specifications described in detail above (Section 9.2.3). The PET scan needs to be done within the same institution on the same scanner (or, if this is not feasible, on the same model PET scanner) used for the pre-treatment PET. A post-treatment PET scan will be done 24-96 hours following completion of RFA, and again at 6, 12, 18, and 24 months after the completion of RFA. Response assessment utilizing both the CT and PET data will be done. For qualitative assessment of the PET images, response criteria similar to those previously described by MacManus, et al. will be used [MacManus MP, Hicks RJ, Matthews JP, et al. 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*. 21: 1285-92, 2003]. Visual assessment of response will be used, as follows: • **Complete metabolic response:** No evidence of FDG uptake in the tumor or activity similar to that in the mediastinum • **Partial metabolic response:** Appreciable reduction in the intensity of tumor FDG uptake or tumor volume apparent to the nuclear medicine physician when pre- and post-treatment PET scan are compared, with no evidence of disease progression • **No metabolic response:** No appreciable reduction in the intensity of tumor FDG uptake or tumor volume apparent to the nuclear medicine physician when pre-and post-treatment PET scans are compared, with no evidence of disease progression • **Progressive metabolic disease:** Appreciable increase in the intensity of tumor FDG uptake or tumor volume apparent to the nuclear medicine physician when pre- and post-treatment PET are compared or with evidence of disease progression at other sites The qualitative visual assessment of response may be guided by the semi qualitative analysis as follows. A complete metabolic response is defined as resolution of abnormal FDG uptake (SUV-max <2.5 in lesion area >1.5 cm). Partial metabolic response is defined as a greater than 20% decrease in SUV-max from the baseline scan or significant decrease in size of lesion that is still metabolically active. Stable metabolically active disease is defined as an SUV-max decrease less than 20% but no increase greater than 20%. Progressive metabolically active disease is defined as identification of new lesions, increase in lesion size, or interval increase in SUV-max by.>20%. The interpretation of the scans will be done with full knowledge of the CT findings on dedicated scanners and with the accompanying CT for PET/CT as this improves the accuracy of the interpretation of the PET study. The finding of either no metabolic response or of progressive metabolic disease on the 6-month post-RFA or subsequent PET scans will be considered suspicious for recurrence and require biopsy when clinically appropriate.
04/28/2006	**Page 18**	**Quality Control Of Procedure and Images:** **Changed From:** "Quality Control will be established to monitor compliance with protocol specifications. The Study Chair and a panel of three additional Site Principal Investigators will review all studies from all institutions. The pertinent captured images from the treatment CT showing the RFA electrode placement and the recorded RFA generator parameters (e.g. impedance, current, power, treatment time and maximum intra-tumoral temperature) will be reviewed by at least two individuals from the quality control panel. The contrast CT studies will be analyzed for six quality control measures: adequacy of contrast administration, proper field of view, collimation, appropriate tumoral coverage, lack of patient motion, and proper window and level display. PET images will be analyzed for quality of contrast, coverage of region, lack of artifacts, and SUV measurements obtained of all appropriate areas of abnormal increased activity. This will allow deviations from protocol to be detected at the earliest possible time. Studies that do not meet quality standards will result in notification of the institutional site radiologist by the Study Chair.

<table>
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<td>The site will be asked to submit a plan for rectifying any systemic problem.
The RFA treatment will not be considered a technical success until the QA panel agrees upon adequate electrode placement and treatment parameters for each patient. Technical successes and failures will be recorded. Sites with any technical failures will be contacted and any deviations from the treatment protocol will be explained to the site investigator. A total of 2 technical failures at any one participating site, based upon operator deficiencies as determined by the consensus of the panel, will lead to mandated withdrawal of the site physician from the study.

Changed To:
“Quality Control will be established to monitor compliance with protocol specifications. The pertinent captured images from the treatment CT showing the RFA electrode placement and the recorded RFA generator parameters (e.g. impedance, current, power, treatment time and maximum intra-tumoral temperature) will be reviewed by at least two individuals from the quality control panel. In addition the contrast CT studies will be analyzed by a panel of 2 individuals from the protocol team including one radiologist with thoracic imaging expertise for six quality control measures: adequacy of contrast administration, proper field of view, collimation, and appropriate tumoral coverage, lack of patient motion, and proper window and level display. Studies that do not meet quality standards will result in notification of the institutional site radiologist by the Study Chair. The site will be asked to submit a plan for rectifying any systemic problem.
The RFA treatment will not be considered a technical success until the QA panel agrees upon adequate electrode placement and treatment parameters for each patient. Technical successes and failures will be recorded. Sites with any technical failures will be contacted and any deviations from the treatment protocol will be explained to the site investigator. A total of 2 technical failures at any one participating site, based upon operator deficiencies as determined by the consensus of the panel, will lead to mandated withdrawal of the site physician from the study.”</td>
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<td>04/28/2006</td>
<td>Page 21</td>
<td>Statistical Considerations:
Changed From:
“Study Design/Endpoints
ACOSOG Z4033 consists of a single arm pilot trial. The study will accrue 55 patients with the anticipation that 53 eligible patients will be accrued. A monthly accrual of 5 eligible patients is expected, with a resulting projected time of 20 months to reach the total accrual goal.
The primary endpoint is time to local recurrence at 2 years. It is assumed that the study regimen will not be of further interest if the 2-year local recurrence free rate is 30% or lower. It is also assumed that a 2-year local recurrence free rate of 50% or higher would be of interest. Because of the long-term follow-up required for each patient, we will use a single-stage design (rather than the standard two-stage design) to differentiate between a 2-year time to local recurrence of 30% and 50%.
Fifty-three eligible patients will be accrued. If 22 or more patients are free of local recurrence over 2 years, then the regimen will be concluded to be efficacious. If 21 or fewer of the 53 patients are free of local recurrence over 2 years, then the regimen will be concluded to not be efficacious. The specific design characteristics are summarized in the following table:

<table>
<tr><td>If the true 24-month time to local recurrence is:</td><td>30%</td><td>35%</td><td>40%</td><td>45%</td></tr>
<tr><td>Probability of declaring efficacy is:</td><td>0.049</td><td>0.197</td><td>0.463</td><td>0.741</td></tr>
</table>

Although the study is designed based on the binary outcome (i.e. local recurrence status at 2 years), the final analysis for the time to local recurrence data will be done using a Kaplan-Meier curve.
One of the secondary endpoints is to estimate the prevalence of toxicity with grade 4 or higher attributed to the study treatment. The toxicity data will be reviewed after every 10 patients become evaluable for toxicity data. The true toxicity will be considered to be significantly higher than 10% if the observed number of toxicities is larger than or equal to 4/10, 6/20, 7/30, 9/40, and 10/53. This monitoring rule has a 5.8% chance of rejecting the study regimen due to excessive toxicity when the true toxicity rate is 10%, and a 90% chance when the true toxicity</td>
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rate is 25%.
Toxicity and local and distant disease control data will be summarized using contingency tables. No single medical center may enter more than 30% of the patients (n=15) into this study."

Changed To:

Up to 20 sites will be allowed to initially enroll up to 2 patients. When a site enrolls their first patient, the RFA images and data for the patient will be reviewed by an expert panel. If the procedure is rated successful, the site can enroll their second patient. Again, the RFA images and data will be reviewed for this patient by the expert panel. If both patient procedures are determined to be technical successes, the site will be deemed "qualified" for this trial. If the second procedure was deemed unsuccessful, the expert panel will determine whether the site is qualified based on the nature of the failure. If the procedure for the first patient is rated unsuccessful, feedback will be provided to the site for the purposes of technically improvement of the procedure prior to the enrollment of the second patient. If the second patient procedure is rated successful, the site will be deemed "qualified" for this trial. If the first patient procedure was rated unsuccessful and the second patient procedure also rated unsuccessful even after feedback received for technically improvement for performing the procedure, the site will be deemed "unqualified" for this study and not allowed to enroll any more patients. The first 2 patients of any "qualified" site will be used in evaluation of efficacy endpoint, the proportion of patients alive at 2 years.

Primary Endpoint

The primary endpoint is overall survival at 2 years. The RFA procedure will not be considered of interest if the 2 year survival rate <= 30% and will be considered of interest if it is > 50%. (The overall 2 year survival rate for RT in a similar population was reported to be 51%, [Bradley, 2003]. Due to the need to follow all patients for 2 years before assessing them for this endpoint of interest we will not perform an interim analysis for this endpoint. If 22 or more of the 55 evaluable patients from a site deemed qualified are alive at 2 years this procedure will be considered promising for further development. If 21 or less are alive at 2 years, this procedure will be considered ineffective in this patient population.

Assuming that the number of deaths is binomially distributed, the significance level is 0.07 and the probability of declaring that this regimen warrants further studies (i.e. statistical power) under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true 2 year overall survival rate is:	30%	35%	40%
then the probability of declaring that the procedure warrants further studies is	.07	.26	.55

Secondary Endpoints and Analysis

The overall time to local failure will be defined as the time from registration to documentation of local failure. The distribution of time to local failure will be estimated using the cumulative incidence method accounting for distant recurrence and death as a competing risk. Local recurrence will be defined as: recurrence in the same lobe or hilum (N1 nodes) or progression at the ablated site after treatment affects have subsided.

The overall time to recurrence is defined as the time from registration to documentation of disease recurrence. If a patient dies without a documentation of disease recurrence, the patient will be considered to have had tumor recurrence at the time of their death unless there is sufficient evidence to conclude no recurrence occurred prior to death. The distribution of time to recurrence will be estimated using the method of Kaplan-Meier.

The proportion of technical success will be estimated by the number of patients with a RFA procedures deemed a technical success divided by the total number of RFA procedures attempted from the qualified sites. Confidence intervals for the true success proportion will be calculated using the EXACT method.

The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine any adverse event patterns. This will be done overall and for just those sites deemed qualified after expert review.

		To explore the impact of imaging techniques of RFA on overall survival and recurrence rates, a cox proportional hazards model will be constructed. Lesion growth, CT-densitometry measurements and FDG-PET activity (in early and follow-up setting) will be used. This analysis will be exploratory in nature as sample sizes will be relatively small. To explore the effect of RFA pulmonary function, the difference in pulmonary function from baseline (pre RFA) and 3 months post RFA will be computed for each patient and a Wilcoxon Sign Rank Test or paired t test will be computed (whichever is more appropriate based on the distribution of the data) to evaluate if the overall change is significantly different from 0. This will also be done at 24 months post RFA to assess the more long term effects of RFA on pulmonary function. A sensitivity analysis will be conducted to evaluate the effects of any missing data on the overall findings.
04/28/2006	**Page 26**	**Physician Skill Verification:** **Changed From:** "All treating physicians are required to have performed 25 lung procedures as well as 10 RFA ablation procedures including one with the Radionics RFA system. Physicians performing the RFA procedure for the trial will need to complete a skills verification form prior to participation (appendix 16.5). **Changed To:** "All treating physicians or treatment teams (if a radiologist and surgeon are both participating in the procedures) have performed 25 static or dynamic image guided thoracic procedures as well as 10 lung RFA ablation procedures with at least one with the Valley Lab system. If there are less than 10 RFA lung procedures then a minimum of 5 procedures and attendance at a CME approved course in RFA is required. All credentialing forms (Appendix 15.4) will be reviewed by the PI and Surgical Co-PI.
04/28/2006	**Page 26**	**Performance Monitoring:** **Deleted:** "If, based upon the materials submitted, or during participation on this study, an issue arises concerning investigator conduct or performance, the ACOSOG Study Committee will review the issues and make recommendations based on its findings to the investigator. It is expected that in most cases, the Study Committee will work with the investigator to improve performance. The Group Chair is empowered to suspend protocol participation, if necessary."
04/28/2006	**Page 27**	**References:** Updated to match protocol, Added Bradley 2004, Dupuy 2006, Vansteekiste 2004 Deleted Dupuy 2003, Zagoria 2001, Campa 2003, Wang 2003
04/28/2006	**Page 31**	**Physician Questionnaire:** Updated to obtain necessary protocol information
04/28/2006	**Page 33**	**QOL Questionnaire** **Deleted:** QOL pages 33 - 39
04/28/2006	**Page 33**	**ICF:** **Deleted from the ICF:** • On the day of your radiofrequency treatment, an *Intravenous Tube* (a tube that goes into your vein) will be placed. You will be given sedation and medicines through this Intravenous Tube (also called an *IV*) to reduce any discomfort you might have during the procedure. • You will need to lie still on your stomach or back for about one hour during the treatment. • You will be given an injection of a medicine that will "numb" the area where the procedure will take place, in order to reduce discomfort. • Padding will be placed on your chest or back to "ground" you (this is process which helps keep you safe while electricity is being used). • After the procedure is finished, you will need to stay in the hospital or clinic for about 4 hours. While you are in the hospital, the doctor and the staff will make

		sure that any pain you have is being treated, and that you are recovering safely from the medicine given to sedate you.
04/28/2006	**Page 33**	**ICF** **Changed From:** "Within 24 to 48 hours of finishing the Radiofrequency Ablation procedure, you will be given a PET scan. This PET scan is being done as part of the research for this study and is not a part of the normal standard of care. You will be asked to return to hospital or clinic for some follow-up procedures. You will be asked to return at 3, 6, 9, 12, 18, and 24 months after your procedure to be given a CT scan. At the 6, 12, 18, and 24-month visits, you will also be given a PET scan. At the 3, 6, 12, and 24-month visits, you will be asked to fill out questionnaires about how well you can breathe, or any difficulty you may have had breathing, as well as a questionnaire about your general health and well-being." **To:** "Within 24 to 96 hours of finishing the Radiofrequency Ablation procedure, you will be given a PET scan. This PET scan is being done as part of the research for this study and is not a part of the normal standard of care. You will not be billed for this 24 to 96 hour PET scan. The other imaging test procedures are part of normal care and will help your doctor assess if your cancer is controlled. You will be asked to return to hospital or clinic for these imaging test follow-up procedures. You will be asked to return at 3, 6, 9, 12, 18, and 24 months after your Radiofrequency Ablation procedure to be given a CT scan and at 6, 12, 18, and 24-month visits, you will also be given a PET scan. You will be asked to return at 3 and 24 months for pulmonary function testing."
04/28/2006	**Page 34**	**ICF** **Radio Ablation Procedure:** Updated table to match protocol
04/28/2006	**Page 34**	**ICF** **Follow-up Visits:** Updated table to match protocol, deleted QOL & added pulmonary function testing
04/28/2006	**Page 35**	**ICF** **Study Plan:** Updated schema, remove questionnaire information