**American College of Surgeons Oncology Group**

**Radiation Therapy Oncology Group**

# ACOSOG Z4099 / RTOG 1021

## A Randomized Phase III Study of Sublobar Resection (+/- Brachytherapy) versus Stereotactic Body Radiation Therapy in High Risk Patients with Stage I Non-Small Cell Lung Cancer (NSCLC)

**Version A0 Activation Date: 05/02/2011**

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## Participants

- **American College of Surgeons Oncology Group members**
- **Radiation Therapy Oncology Group members**
- **Cancer Trials Support Unit (CTSU) investigators**

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# 1 Introduction

## 1.1 Background and Rationale

Stage I (T1-2, N0, M0) lung cancer has historically been a predominantly surgically treated disease. While surgical resection with lobectomy or pneumonectomy is the established first line standard of care treatment for stage I NSCLC with cure rates of 65-90% [2-4], some patients such as those with compromised cardiopulmonary reserve are debilitated by the operation and post-operative course. As such, stage I patients can be divided into 3 categories based on their pre-existing medical history: 1) standard risk operable (can likely tolerate lobar resection or pneumonectomy); 2) High-risk operable patients (can likely tolerate sublobar resections but not the 1st line lobar resection or pneumonectomy); and 3) medically inoperable (unable to tolerate any form of lung resection)

For high-risk operable patients (category 2), the usual approach is sublobar resection (SR) which can be either an anatomical segmentectomy or a non-anatomical wedge resection. It is generally considered, however, that sublobar resections are a compromise compared to lobectomy because of increased locoregional failure [2,19]. Experience with conventional radiotherapy [5,6] and stereotactic body radiation therapy (SBRT) [7-13] has been primarily with non-surgical candidates (category 3). For the inoperable group, SBRT has shown extremely high rates of primary tumor control, low toxicity, and better than historical survival including the recently reported RTOG 0236 trial which had 98% 3-year primary tumor control, 91% primary and involved lobe (local) control, 87% local-regional control, modest grade 3 or higher toxicity (16%) and 3-year overall survival of 56% [14] justifying SBRT as a new standard of care for medically inoperable patients. Increasingly non-resectional therapies such as SBRT are being used for high-risk operable patients (category 2). The impetus for this is the lower toxicity profile of SBRT compared to SR, and the perception that local recurrence rates following SBRT may even be equivalent to those of lobectomy.

A key issue that must be considered when comparing these modalities based on available literature is that the definitions of local recurrence, local control, and regional recurrence are not uniform. This has led to different perceptions and interpretations of the published literature relating to these modalities. In the surgical literature, local recurrence variably includes recurrence occurring within the same lobe, sometimes another lobe within the same ipsilateral lung, hilar and sometimes ipsilateral mediastinal lymph nodes [2,18, 102]. In the SBRT literature, local recurrence usually is synonymous with primary tumor control, i.e., limited to recurrence within and sometimes within 1cm of the planning treatment volume (PTV) [12,101]. The more appropriate convention for characterizing recurrence definitions is a reflection on the original TNM staging. As such, a recurrence of the original primary tumor (originally characterized by the T of the TNM staging including the primary tumor and involved lobe) is deemed a local recurrence. A recurrence in the primary tumors draining lymph nodes (hilar and mediastinal as originally characterized by the N of the TNM staging) is deemed a regional recurrence. Finally, a recurrence in distant sites (originally characterized by the M of the TNM staging) is deemed a disseminated recurrence. By this convention, both the more recent surgical literature and SBRT literature have been guilty of inappropriate recurrence definitions making comparisons difficult.

Better therapies are needed for high-risk operable patients (category 2). To address the higher rate of staple line recurrence associated with SR (particularly non-anatomic wedge resections) while hopefully maintaining a more tolerable profile than lobar resections, several groups have added additional local treatment with interstitial brachytherapy implanted at surgery [16,18,21,22,113,114] . These reports show that local recurrence appears to decrease with brachytherapy with little additional morbidity. An ACOSOG trial (Z4032) aiming to confirm the improvement in local control as well as assess overall survival in this high risk population has recently completed accrual. Until the primary-endpoint (local recurrence) results of this study are available, adjuvant brachytherapy should not be considered the standard approach with SR. Other factors that have been demonstrated to minimize local failure after SR include the use of segmental in preference to wedge resection, and care to ensure that margins of at least 1 cm from the tumor to staple line, or margin/tumor diameter ratio of 1 or more [12,18,102,103] are achieved.

Coincident with the evaluations of SR with brachytherapy have been investigations into the use of SBRT in operable patients [115-117]. The RTOG is currently evaluating the role of SBRT in a phase II trial of operable patients (RTOG 0618) which completed accrual in 2010 [116].

**Outcomes in T1N0M0 NSCLC patients**

| Treatment (with references) | Patient Category | Local Control | 3-year Overall Survival |
|---|---|---|---|
| Lobectomy/Pneumonectomy [2, 13, 16, 19, 105, 106, 110, 111, 121, 122, 123] | Standard risk operable | 95+% | 75-90% |
| Sublobar resection [2, 13, 16, 19, 105, 106, 110, 111, 121, 122, 123] | Standard risk operable | 75-95%^ | 61-90% |
| Sublobar resection [15, 18, 22, 124] | High risk operable | 75-95%^ | 60-80% |
| Sublobar+brachytherapy [15-22] | High risk operable | 90-95+% | 65-80% |
| SBRT [118] | High risk operable | 90%* | ?? but likely at least 56% |
| SBRT [7, 14] | Medically inoperable | 90%* | 56% |

^ Usually includes local nodal disease and intralobar parenchymal recurrence in surgical series

* Includes intralobar parenchymal recurrence but does not include regional failure (gross rate 4% in RTOG 0236)

There have not been any prospective, randomized trials to compare the efficacy or the toxicity profile of SR to SBRT in high risk patients. Currently, it is difficult to make comparisons between the therapies for several reasons: 1) There may be some selection bias with less healthy patients being treated with SBRT, potentially confounding efficacy determinations. 2) Most surgical studies that have been published on SR have not used Common Toxicity Criteria for reporting morbidity. This may lead to over-reporting of complications. For instance a common post-operative complication after thoracic surgery is atrial fibrillation. However in most cases this would be a grade 2 complication and only be classified as grade 3 if the atrial fibrillation was incompletely controlled medically or required a device for control. 3) Most surgical series will only report 30-day mortality, and rarely mortality occurring at longer follow-up. A recent report of SBRT demonstrated a 7.14% incidence of grade 5 toxicity, with most deaths occurring many months or years after treatment was completed [8]. In this same study of 70 patients there were 7 (10%) grade 3 or 4 toxicities. A large study of 182 patients undergoing segmental resection demonstrated complications in 59 (32.4%) of patients of which 24 (13.2%) were considered major [103]. It is unclear for the reasons stated above how many complications would have been graded as 3 or higher. This randomized study will allow us to make comparisons in a homogenous patient group. The Charleson Co-morbidity Index can be used to characterize general health between comparison groups, providing a risk-profile.

A randomized comparison study between SR and SBRT in high risk patients would significantly improve our understanding of the differences between these modalities by using the same definitions of recurrence and toxicity in a similar risk patient group that will be randomized after tissue diagnosis is obtained and on the basis of clinical staging. A potential concern is that there will be patients with unsuspected N1 or N2 disease who will be identified in the SR group. These patients will continue to be followed, since this study will use initial clinical staging and an "intention to treat" analysis. It is thought that the local recurrences rates and possibly regional and distant recurrence rates will likely differ between the two modalities. Currently, while SBRT primary tumor control is impressive, the overall survival rate for high risk operable (category 2) patients is unknown. The survival results of RTOG 0618 will not be available for several years. For the reasons given above, it is reasonable to anticipate that the standard of care, SR, may have improved overall survival compared to SBRT. However, SBRT is a less invasive and better tolerated (i.e. less morbidity) intervention than SR, which might make it a more attractive option for selected patients as treatment than SR even if it is less efficacious. We intend to collect high level evidence about the performance of both treatments such that patients can make better informed decisions regarding options when facing this disease.

There has been some variation in dose and fractionation for SBRT in published reports. This trial will use the dose established in RTOG 0236 and 0618 for the SBRT arm on this trial building on their multicenter prospective experience, data collection for 3 fractions, and excellent control/toxicity ratio. The SR arm will allow SR to be performed with and without brachytherapy.

**Z4032 Results**

It is anticipated that the results of Z4032, comparing the local recurrence free survival (LRFS) rates of SR versus SR plus brachytherapy, will be mature in 12/2011. If it appears one arm of Z4032 is superior to the other arm, the present trial will be amended to mandate that the superior SR treatment be used in the SR arm of the trial. At that time, we may also adjust the sample size if the three year overall survival (OS) rate for the SR arm appears to differ considerably from 80%. If neither arm of Z4032 is declared superior, we will continue to allow the choice of including brachytherapy or not as part of the treatment on the SR arm for this trial.

Although the outcome data for Z4032 are not yet mature, there is information available regarding 30-day adverse events and mortality rates for the two treatment arms. The table below summarizes the 30-day adverse event (regardless of attribution) and mortality rates by arm, i.e. the SR and the SR plus brachytherapy arms. The table indicates the number of patients (and percent) that had at least one adverse event of the indicated grade range within 30 days from surgery.

| | **SR N = 114** | | **SR + brachytherapy N = 109** | |
|---|---|---|---|---|
| **Adverse event grade** | N | % | N | % |
| Grade 3+ | 29 | 25.4 | 33 | 30.3 |
| Grade 4+ | 8 | 7.0 | 8 | 7.3 |
| Grade 5 | 1 | 0.9 | 2 | 1.8 |

The 30-day adverse event and mortality (i.e. Grade 5 adverse event) rates are similar between the two treatment arms.

**Sublobar Resection Studies**

In 1995, the Lung Cancer Study Group published the results of a randomized study comparing SR to lobectomy [2]. The principal finding was an increase in loco-regional recurrence in the SR group of 17.2% compared to 6.4% in the lobectomy group. As a result SR is reserved in most centers as a compromise operation for the high-risk patient with NSCLC. In the Lung Cancer Study Group study locoregional recurrence was defined as recurrence at or near the primary site (i.e., within the same lung) and the ipsilateral mediastinum and hilar lymph nodes. Another multicenter retrospective study published two years later demonstrated local recurrence rate of 13.7% after SR [19]. In contrast to these North American studies, there is a growing body of literature from Japan favoring the use of segmentectomy for small peripheral lung cancers. Two such studies have demonstrated low local recurrence rates 4.9% and 2.7% respectively, similar to that seen after lobectomy [105, 106]. Local recurrence rates have also been demonstrated to be decreased with the use of adjuvant brachytherapy to 3.3% in limited retrospective studies [18]. This approach is currently being investigated in Z4032, a phase III study.

Studies of SR, have generally involved longer follow-up and larger patient numbers than studies of SBRT. In the Lung Cancer Study Group study [2] there was a minimum follow-up of 4.5 years. Overall 1 and 2 year survival were 95% and 80% respectively after SR. In a Japanese study involving 262 patients 1 and 2 year survival rates were 98% and 96% respectively, however this study included patients who were candidates for lobectomy who would be expected to have better survival than the high-risk operable group that will be the focus of this study [105]. A more recent North American study of 182 patients (which did include high-risk as well as standard-risk operable patients) also demonstrated good survival at 1 and 2 years of 94% and 90% respectively [103].

**Stereotactic Body Radiotherapy Studies**

Numerous studies from several continents have been reported on this technique in early stage lung cancer. The earliest prospective phase I study from Indiana University demonstrated the safety of a 3 fraction regimen and local tumor control dose response of SBRT at increasing radiation doses [10]. A subsequent phase II study for stage I tumors up to 7 cm using a dose of 20-22 Gy x 3 fractions with inoperable NSCLC was recently updated [8]. Kaplan-Meier primary tumor control at 3 years for the 70 patients was reported as 88.1% and 3 year overall survival was 42.7%. Regional (nodal) and distant gross rates of recurrence were 8.6% and 12.9%, respectively. This study treated both central and peripheral tumors indiscriminately and

found significantly more toxicity, including toxic deaths, with central tumors using the 3 fraction regimen [12]. A prospective phase II multicenter trial from Scandinavia treated 57 medically inoperable patients with SBRT at 15 Gy X 3 fractions [7]. With a median follow-up of 35 months, the authors reported 3-year Kaplan-Meier primary tumor local control of 92%. A total of 3 patients had regional relapse. The Kaplan-Meier 3-year overall survival was 60%. Studies using lower SBRT dose potency show both increased primary tumor, local, and regional failure. For example, a study from the University of Pittsburgh using only 20 Gy in a single fraction resulted in a very high gross rate of loco-regional failure of 42% justifying the considerably higher doses used in the aforementioned studies [107]. Another example of problems with inadequate dose is demonstrated by a study from Germany which used only 15-24 Gy in a single fraction to the edge of the target resulting in a disappointing 32% Kaplan-Meier local failure rate at 3 years with an additional 4/42 patients failing in the regional lymph nodes [108]. A frequently cited study from Japan demonstrated superior local control in patients treated to > 100Gy [101]. In this study overall local recurrence occurred in 14% but was reduced to 8.4% when tumors were treated to > 100Gy. However it should be noted that parenchymal recurrence within the same lobe away from the primary tumor site and regional lymph nodes were not included in their definition of local recurrence. An additional 6.9% of patients had failure within the regional lymph nodes among those treated with 100Gy. Median follow-up in this study was 24 months. Review of the survival curves demonstrates 1 and 2 year survivals of 85% and 65% for patients treated with < 100Gy and 90% and 75% for patients treated with greater than 100Gy. It should also be emphasized that unlike other published SBRT studies, this included patients who were good surgical candidates and could have undergone lobectomy, again confounding the interpretation of these data for specifically high risk patients. The Radiation Therapy and Oncology Group recently reported on RTOG 0236, a phase II trial of SBRT using a total dose of 54Gy in 3 fractions (based on the Indiana University experience), which treated 55 patients [14]. Primary tumor failure (defined as enlargement of at least 20% on CT and either biopsy or PET activity similar to pre-treatment value) was 2% at three years. Three-year estimated overall survival was 56%. Protocol specified Grade 3 and 4 toxicity occurred in 16% of patients.

SBRT is a technologically intensive therapy with numerous delivery variables that may affect outcome, requiring a high level of quality assurance monitoring to ensure uniform treatment. In addition, proper training of physicians and staff is imperative to achieve optimal outcomes given the unique radiobiology of SBRT apart from conventional therapy [23]. As an example, the phantom radiation requirements for accreditation in RTOG 0236 brought to light a critical issue for quality SBRT relating to treatment planning. Sites using tissue heterogeneity correction algorithms solely accounting for attenuation (not scatter) delivered significantly erroneous doses compared to expectations [24]. The high compliance success of RTOG 0236 and the ongoing RTOG protocols is directly related to this comprehensive quality assurance process.

## 1.2 Significance

The proposed patient study group represents a cohort of patients with greater than average risk, with potentially curable stage I NSCLC. In the surgical group, there is greater risk involved, but patients are more likely to achieve complete control of their primary tumor (assuming complete resection is performed), thus alleviating the need for further future treatment. Additionally local lymph nodes will be removed. This may provide better local control and also identify patients who may have occult N1 or N2 disease, who would benefit with additional therapy. In the SBRT group, morbidity should be reduced initially, but the chance of complete local control of the primary tumor will be lower than with resection perhaps requiring further treatment. Since these patients are greater than average risk, these oncological differences may not be as important clinically, particularly since many of these patients may already be impaired particularly from a pulmonary standpoint.

Clearly it is difficult to make definitive comparisons between these therapies, since end-point definitions vary in these studies, as does the delivery of SBRT. Additionally there may be some selection bias with sicker patients being referred for SBRT instead of SR. For this reason we believe this randomized study is needed and that there will be clinical equipoise in this high-risk group of patients.

This study is important in that not only will we learn information about the true oncologic differences between these therapies, we will also determine the relative impact of these therapies on pulmonary function and quality of life.

## 1.3 Objectives

### 1.3.1 Primary Objective

To ascertain whether patients treated by SBRT have a 3-year overall survival (OS) rate that is no more than 10% less than patients treated with SR.

### 1.3.2 Secondary Objectives

- To compare loco-regional recurrence-free survival between study arms. See Evaluation of Outcomes (Section 7) for recurrence definitions.
- To compare disease-free survival between study arms.
- To compare grade 3 or higher specific adverse event profiles between study arms; specific comparisons will include AEs at 1, 3, 6 and 12 months post therapy.
- To compare pulmonary function between patients treated with SBRT and patients treated with SR.
- To compare the adverse events and PFTs in each arm for patients with low or high Charlson comorbidity index scores, including a test interaction between Charlson comorbidity index scores (low vs. high) and treatment arm.

### 1.3.3 Correlative Science Objectives

- To compare the quality-adjusted survival between the treatments SBRT and SR in terms of time to death (primary) and time until recurrence (secondary).
- To examine whether pre-operative and post-operative clinically significant deficits in previously-identified prognostic PRO domains (overall QOL, fatigue, anxiety, dyspnea) are associated with shorter patient survival in this patient population and to compare the relative effectiveness of each treatment (SBRT and SR).
- To contribute to an ACOSOG bank of normative data in order to improve short/long term outcomes of cancer patients by identifying patients experiencing clinically significant deficits in patient-reported outcomes and the relationship to genetic variables.
- To explore whether blood based biomarkers, including osteopontins, will be able to predict which patients will be at high risk for recurrence by treatment with either SBRT or SR.
- To explore whether blood based biomarkers, including TGF-β1, will be able to predict which patients will be at high risk for pulmonary complications by treatment with either SBRT or SR.

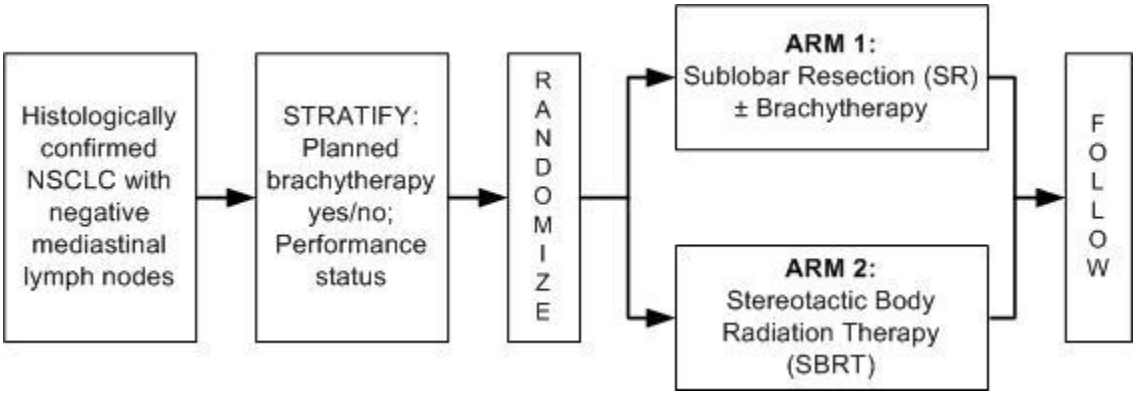
## 1.4 Study Design

This is a prospective, randomized Phase III trial comparing SR and SBRT for high-risk patients with operable lung cancer.

### 1.4.1 Accrual Goal

Target accrual for this study is 420 patients, with a projected accrual rate of 6-10 patients per month.

## 1.5 Schema




# 2 Patient Selection

**Each eligibility criterion must be evaluated and documented in the patient's medical record. No eligibility exceptions are permitted.**

## 2.1 Eligibility Criteria

1. Age ≥ 18 years.
2. ECOG performance status (PS) 0, 1, or 2.
3. Biopsy-proven non-small cell lung cancer (NSCLC).
4. Tumor ≤ 3 cm maximum diameter, clinical stage Ia or selected Ib (i.e., with visceral pleural involvement) by PET/CT scan of the chest and upper abdomen performed within 60 days prior to registration.
5. All clinically suspicious mediastinal N1, N2, or N3 lymph nodes (> 1 cm short-axis dimension on CT scan and/or positive on PET scan) confirmed negative for involvement with NSCLC by one of the following methods: mediastinoscopy, anterior mediastinotomy, EUS/EBUS guided needle aspiration, CT-guided, video-assisted thoracoscopic or open lymph node biopsy.
6. Tumor verified by a thoracic surgeon to be in a location that will permit sublobar resection.
7. Tumor located **peripherally** within the lung. NOTE: Peripheral is defined as not touching any surface within 2 cm of the proximal bronchial tree in all directions. See the diagram in Section 2.2. Patients with non-peripheral (central) tumors are NOT eligible.
8. No evidence of distant metastases.
9. PFTs with DLCO within 90 days prior to registration.
10. Patient at high-risk for surgery by meeting a minimum of one major criteria or two minor criteria as described below:

    **Major Criteria**

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

    **Minor Criteria**

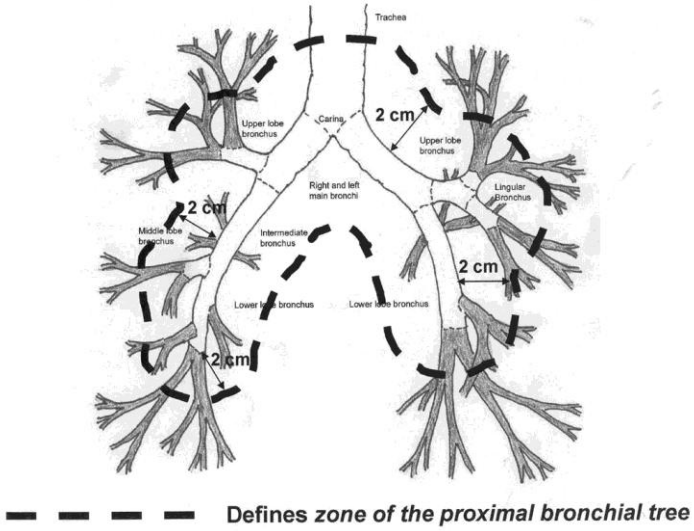
    - Age ≥75
    - FEV1 51-60% predicted
    - DLCO 51-60% predicted

- Pulmonary hypertension (defined as a pulmonary artery systolic pressure greater than 40mm Hg) 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 ≤ 55 mm Hg or SpO2 ≤ 88%
- pCO2 > 45 mm Hg
- Modified Medical Research Council (MMRC) Dyspnea Scale ≥ 3.

| 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 |

11. No prior intra-thoracic radiation therapy. NOTE: Previous radiotherapy as part of treatment for head and neck, breast, or other non-thoracic cancer is permitted. Previous chemotherapy or surgical resection for the lung cancer being treated on this protocol is NOT permitted.
12. Non-pregnant and non-lactating. Women of child-bearing potential must have a negative urine or serum pregnancy test within 60 days prior to registration. Peri-menopausal women must be amenorrheic ≥ 12 months prior to registration to be considered not of childbearing potential.
13. No prior invasive malignancy, unless disease-free for ≥ 3 years prior to registration (exceptions: non-melanoma skin cancer, in-situ cancers).

## 2.2 Proximal Bronchial Tree Diagram (from RTOG 0236)




## 2.3 Staging Criteria

Patients will be staged according to the 7th edition of AJCC Cancer Staging Manual, 2010. See the staging reference in the Appendices.

# 3 Study Calendar

| **Tests and Observations** | Within 60 days prior to reg. (except where noted) | After reg. and before SBRT or surgery | **ARM 1 (SR)** | | **ARM 2 (SBRT)** | | **BOTH ARMS (From date of surgery/end of SBRT)** | | | | | | | | | | | At time of disease relapse / PD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | At time of surgery | 4 weeks post-op | Before final SBRT (same day) | 4 weeks after SBRT | 3 mo. | 6 mo. | 9 mo. | 12 mo. | 15 mo. | 18 mo. | 21 mo. | 24 mo. | 30 mo. | 36 mo. | Yearly to 5 years | |
| Credentialing | X[1] | | | | | | | | | | | | | | | | | |
| History & Physical, ECOG/Zubrod PS | X | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pregnancy test | X[2] | | | | | | | | | | | | | | | | | |
| Tumor biopsy (and LN biopsy, if needed) | X | | | | | | | | | | | | | | | | | X[9] |
| Pulmonary Function Tests | X[3] | | | | | | X | X | | X | | | | X | | | | |
| PET/CT scan chest/upper abdomen | X | | | | | | | X | | X | | | | X | | X | X | X[9] |
| CT scan chest/upper abdomen | | | | X[7] | | | X | | X | | X | X | X | | X | | | X[9] |
| Adverse event assessment | | X | | X | | X | X | X | X | X | | | | | | | | |
| Charlson Comorbidity Index | | X | | | | | | | | | | | | | | | | |
| Blood specimen collection[4] | | X[5] | | X | X | | | X | | X | | X | | X | | X | X | |
| Tissue specimen collection[4] | | | X | | | | | | | | | | | | | | | |
| EQ-5D, LCSS, LASA, UCSD SOB questionnaires | | X | | X | | X | X | X | | X | | | | X | | | | |
| QA submission to ITC | | X[6] | | X[8] | | X[8] | | | | | | | | | | | | |
| Image submission to ITC | | | | | | | | | | | | | | | | | | X[9] |

1 Credentialing for surgery, brachytherapy, and SBRT may be completed any time prior to first registration. See Credentialing (Section 12).

2 For patients of childbearing potential.

3 Baseline PFTs are required within 90 days prior to registration. PFTs must include routine spirometry and DLCO. Arterial blood gases are not required but may be used as minor criteria for study enrollment. See Eligibility Criteria (Section 2.1).

4 Specimen collection is required for consenting patients only. See Biospecimen Collection (Section 13).

5 Pre-treatment blood specimen may be collected at the time of surgery for patients being treated on Arm 1.

6 Submission to ITC of the first patient's treatment plan is required prior to treatment for each type of SBRT system used at a site. See Quality Assurance Requirements (Section 5.4).

7 Post-implant CT scan is required for Arm 1 patients receiving brachytherapy.

8 See Quality Assurance Requirements (Section 5.4).

9 PET/CT is required to confirm disease relapse/progression (i.e., if CT scan alone is suspicious for relapse/progression, then PET/CT is required to confirm disease status). Biopsy of relapse/progression sites is highly recommended but not required. Submission of biopsy pathology report (if applicable) and scan reports is required. Submission of imaging is required in the absence of a tissue diagnosis, and also may be requested as needed by the study team on a case-by-case basis. See Evaluation of Outcomes (Section 7). After disease relapse/progression, patients will be followed for survival and quality of life, as required by the Study Calendar.

## 3.1 Imaging Guidelines

### 3.1.1 CT

CT scans of the chest and upper abdomen will be performed using routine diagnostic imaging protocols (institution-determined). Oral and intravenous contrast agents will be used in the usual manner unless contraindicated (e.g., renal insufficiency, allergic reaction to iodinated contrast). Required CT scans may be obtained as part of a combined PET/CT study. To the extent possible, follow up CT scans on a given patient will be performed using similar imaging protocols, and on the same or similar CT scanner (same manufacturer).

### 3.1.2 FDG-PET/CT

**Equipment**

A dedicated BGO, LSO, LYSO, or GSO PET/CT scanner must be used for the baseline and follow-up FDG-PET/CT studies. The same scanner and scanning protocol should be used for all scans. The PET/CT scanner must be capable of providing attenuation-correction (based either on a radionuclide transmission scan or CT images). For questions regarding whether a particular PET/CT scanner is in compliance with this protocol, investigators may contact the Imaging Co-chair.

**FDG Injection**

Patients must fast for a minimum of 4 hours prior to the injection of FDG (see below). Serum glucose should be obtained and recorded immediately prior to FDG injection, and must be ≤ 200 mg/dL. The administered activity of FDG should be based on the recommendation of the manufacturer of the PET scanner. In general, the recommended FDG dose is 0.14-0.21 mCi/kg, with a total injected dose range of 10-25 mCi.

Note: FDG-PET in patients with diabetes will preferably be scheduled in the morning and instructions for fasting and use of medications will be provided in consultation with the patient's primary physician.

**PET Imaging**

PET imaging should be performed in accordance with the manufacturer's recommendations. The imaging should be performed with the patient supine and with the arms up (unless this cannot be tolerated by the patient). Commercially available devices (i.e. overhead hand grips) are available to facilitate this patient positioning. The patient should empty his/her bladder prior to and immediately following the PET/CT study PET emission imaging should be started 45-90 minutes following FDG injection. For each patient, the time between FDG injection and PET imaging should be similar for the baseline and follow-up PET scans. CT or transmission scans for attenuation-correction of the PET emission images should be obtained according to the manufacturer's recommendations. The emission data must be corrected for scatter, random events, and dead-time losses, and bed positions should be overlapped to reduce artifacts between the bed positions. Image reconstruction and filtering should be performed according to the manufacturer's recommendations, although OSEM techniques are preferred.

# 4 Patient Registration/Randomization

**Prior to patient registration, participating physicians and sites must meet all credentialing requirements. See Credentialing (Section 12).**

Before registering patients, all investigators and study support staff must be members of the Cancer Trials Support Unit (CTSU)). Please see the CTSU website (www.ctsu.org) for details on registering as a CTSU member.

All forms and documents associated with this study can be downloaded from the protocol-specific page of the ACOSOG website (www.acosog.org) or from the Protocols page of www.ctsu.org.

Registration is available 24 hours a day via the CTSU's Oncology Patient Enrollment Network (OPEN) Portal system. All participating sites (ACOSOG and non-ACOSOG sites) will use OPEN to enroll patients to this study. OPEN can be accessed at https://ctsu.org/open/ or from the CTSU members' website OPEN tab.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPPA authorization form (if applicable).
- All pertinent forms and documents are on file with the CTSU.

**Access requirements for OPEN:**

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' website.
- To perform registrations, the site user must have been assigned the 'Registrar' role. ACOSOG members intending to register patients have been assigned a 'Registrar' role on the group's roster.

**Information required at registration:**

- Registering institution and investigator CTEP ID numbers
- Patient demographic and eligibility information (see the registration form)

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print the confirmation for your records. Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In the event of electronic or communication problems, contact the QA Specialist.

## 4.1 Stratification Factors

The following stratification factors will be observed throughout the enrollment period of the study:

- Institutional intent to use brachytherapy: yes vs. no
- ECOG performance status (PS): 0 vs. 1 vs. 2

## 4.2 Treatment Arms

**Arm 1:** Sublobar resection with or without brachytherapy

**Arm 2:** Stereotactic body radiation therapy

# 5 Interventions

**Prior to patient registration, participating physicians and sites must meet all credentialing requirements. See Credentialing (Section 12).**

**All protocol therapy, including surgery, must be performed at the registering site or an affiliated institution with IRB approval for the study.**

## 5.1 Sublobar Resection

For patients randomized to Arm 1, a wedge resection or anatomical segmentectomy will be performed. Ideally, surgery should occur within 30 days after registration/randomization.

Thoracotomy or VATS approach is allowed. A technically successful sublobar resection will be defined as either a segmentectomy or a wide wedge resection with at least a 1 cm margin from the tumor to the staple line, or include the use of brachytherapy (see below). **If a wedge resection alone (without brachytherapy) is performed, intraoperative pathology consultation should be obtained to confirm a 1 cm margin from the tumor to the staple line. This must be documented in the operative report.** Lymph node sampling is recommended but not required.

### 5.1.1 Touch Prep for Staple Line

A touch prep of the specimen will be performed using the run-across method described by Sawabata et al.[131] The cytological examination should be performed before the specimen is cut for histological examination to prevent malignant cell contamination. In those procedures where a frozen section is to be performed to confirm cancer, the touch prep should be performed first for the same reason. A glass slide should be run across the entire staple margin of the specimen **after removal from the thoracic cavity** at least 3 times. The slide should be run over the specimen after it is removed from the patient but before the specimen is cut by the pathologist. The slide does not need to touch the remaining non-resected lung. This slide containing the extracted specimen should be spread on another slide and fixed for cytological examination. A positive margin will be defined as at least 3 malignant cells or clustered malignant cells on the glass slide. **NOTE: Documentation of the staple line touch prep must be included in the final operative and pathology reports.**

## 5.2 Brachytherapy

Patients randomized to Arm 1 may receive brachytherapy at the discretion of the treating physician.

Sites intending to use brachytherapy must complete all credentialing requirements prior to the first patient registration. See Credentialing (Section 12) for required documentation.

NOTE: Prior participation in ACOSOG Z4032, which included successful digital submission of one or more cases, precludes the need for additional brachytherapy credentialing unless there is a change in physicist, radiation oncologist, treatment planning system, or brachytherapy source. Contact the QA Specialist for questions about your credentialing status.

Brachytherapy may be performed using either a mesh or a "double-suture" method at the discretion of the operating surgeon and radiation oncologist. For the mesh patients the following will be performed. The radiation physicist must measure or calculate the amount of emitted radiation delivered to individuals near the implanted patient to ensure that patient isolation measures are not required. This precaution is routinely taken; however, there have not been any patients requiring such isolation to date in over 260 patients treated overall. The radioactive sources must be selected and placed into the patient with a designated radiation therapy physician present.

After securing brachytherapy implant and with lung reinflation, positioning of the sources should be verified visually when feasible.

After the implant is secured, chest tube drainage should be accomplished and the wounds should be closed in a standard fashion.

N**OTE: Digital submission of quality assurance documentation is required for each patient treated with brachytherapy. See Quality Assurance Requirements** (**Section 5.4).**

### 5.2.1 Mesh Brachytherapy

The radiation oncologist and thoracic surgeon estimate the surface area of the implant with an intention to cover the entire length of the stapled margin of resection and a 2 centimeter lateral margin along this linear course. This is accomplished on a sterile back table during the course of the operative intervention. A polyglycolic mesh template is constructed so that each $^{125}$I seed is placed at 1 cm square strand separation intervals along the surface of the mesh implant. Each seed should have an activity of 0.4 – 0.6 mCi. The $^{125}$I seeds are provided within a polyglycolic acid suture thread at 1centimeter intervals along the sutures length. By sewing the thread with the $^{125}$I implants into the polyglycolic acid mesh with the drawn out grid upon it, the radiation oncologist can establish a surface implant with uniform dose distribution.

The brachytherapy implant will then be introduced into the chest through a thoracoscopic access site or the thoracotomy incision by the thoracic surgeon, with the radiation oncologist (authorized user) present. The thoracic surgeon configures the proper topical orientation of the implant over the resection margin, and then and then secures the implant to the visceral pleura with tacking sutures of 2-0 to 3-0 silk or polyglycolic acid suture.

### 5.2.2 Double-suture Brachytherapy

The resection margin should be well defined by sutures or, as in most cases, by a linear row of staples fired from a linear gastrointestinal stapler or an endo stapler. The length of each arm of the resected margin (staple line in most cases) is measured to determine the number of seeds that will be required for that arm. The $^{125}$I seeds embedded in polyglactin 910 suture (Oncura, Princeton, NJ) come in suture strands containing ten seeds at 1 cm center-to-center separation. Each seed should have an activity of 0.7-0.9 mCi. Along each arm of the resected margin, an appropriate length of suture embedded with $^{125}$I seeds will be affixed 0.5 cm on either side of the resection margin measured from the base of the staple or suture line. The seeds are affixed to the lung surface with several sutures of 3-0 silk spaced 1-2 one to two cm apart. The sutures for each strand are put in place before taking the seeds from their protective container. The seeds are then laid in place by the radiation oncologist (or by the thoracic surgeon with the radiation oncologist present) and sutures tied. The process is continued until both sides of each resection margin have a parallel row of seeds on each side. Any excess of seeds should be placed in a lead container.

### 5.2.3 Seed Calibration and Handling

The sources will be received and inventoried in accordance with state and federal regulations. The source strength shall be verified in accordance with current AAPM recommendations (AAPM Report 98, TG-40, TG-56, TG-64). A dosimetry system with direct traceability to either the National Institute of Standards and Technology (NIST) or an Accredited Dosimetry Calibration Lab (ADCL) shall be available for this purpose.

Sources used in this protocol must be listed on the Joint AAPM/RPC Registry of Brachytherapy Sources (http://rpc.mdanderson.org/rpc/).

### 5.2.4 Dosimetry

The goal of the implant is to provide a dose of 100 Gy to 5 mm depth with the mesh technique or 100 Gy to 7 mm depth along the central axis (resection margin) with the double strand technique. Suture seed placement, and thus dose prescriptions, will be determined intraoperatively. These will be dependent on the length of the resection margin. A written dose prescription will include the number of seeds, the number of strands, the activity of each seed, the total activity of the implant and strand separation.

Final dosimetry is obtained after complete re-inflation of the lung with CT-based 3D planning at 4 weeks post-procedure. Contrast is not required. CT slice thickness should be 5mm or less. The Clinical Target Volume (CTV) will be considered the resection suture line. The Planning Target Volume-1 (PTV- 1) will be considered the CTV plus 5mm and the PTV-2 will be CTV plus 7mm.

The dosimetry of the $^{125}$I seeds will be based upon AAPM Report TG 43 as updated in 2004. The vendor's stated source strength shall be used in all dosimetry calculations.

The planning system shall be able to perform structure-based analysis from axial image sets. This shall include isodose display and generation of dose volume histograms. The calculation grid shall be set no larger than 2mm x 2mm x the axial slice width. Calculations shall include dose volume histograms for the CTV, PTV-1, and PTV-2 with dose increments no greater than 1.0 Gy. DVH's shall also be submitted for a 1.0 cm expansion of the CTV and a 2.0 cm expansion of the CTV.

**The planning system must be capable of exporting data as DICOM RT for submission to the Image-guided Therapy Center (ITC). See Quality Assurance Requirements (Section 5.4).**

#### 5.2.5 Brachytherapy Deviation Criteria

Major deviations will be assessed for implants that have dislodged from the resection margin or for total implanted activity that is 10% less than the minimum recommended activity (16 mCi for the mesh technique or 14 mCi for the double suture technique). Minor deviations will be assessed for implants with insufficient total activity to deliver at least 95 Gy to 90% of the PTV.

#### 5.2.6 Brachytherapy Quality Assurance

See Quality Assurance Requirements (Section 5.4).

## 5.3 Stereotactic Body Radiation Therapy

All positioning systems and systems used to account for internal organ motion must be reviewed and approved by the study team before enrolling patients on this trial. See Credentialing (Section 12).

The treatment plan for the first patient to be treated with SBRT must be submitted for review prior to starting protocol therapy. See Quality Assurance Requirements (Section 5.4).

#### 5.3.1 Dose Specifications

##### 5.3.1.1 Stereotactic Targeting and Treatment

SBRT has now been formally defined and described in a published guideline from the American College of Radiology and American Society for Therapeutic Radiology and Oncology. [104] This protocol will respect that guideline. The term stereotactic for the purposes of this protocol implies the targeting, planning, and directing of therapy using beams of radiation along any trajectory in 3-D space toward a target of known 3-D coordinates.. The coordinate system is defined by reliable "fiducials". A "fiducial" may be external or internal to the patient's body. External fiducials may relate to a frame or treatment device. Internal fiducials may be implanted markers or reliably identified anatomy including the tumor itself (e.g., acquiring tomographic views of the tumor simultaneously with the treatment). In all cases, the relationship between the fiducial and the actual tumor position in real time should be reliably understood for both planning and treatment. This differs from conventional radiation therapy, in which therapy is directed toward less-than-reliable skin marks or bony landmarks that may not have an well described relationship in space compared to the soft tissue tumor target.. This protocol will require treatments to be conducted with the use of a fixed 3-D coordinate system defined by fiducials. The coordinate system defined by the fiducials should be directly related to the radiation-producing device (e.g., couch and gantry) in a reproducible and secure fashion. Capability should exist to define the position of targets within the patient according to this same 3-D coordinate system. As such, the patient is set up for each treatment with the intention of directing the radiation toward an isocenter or target according to the known 3-D coordinates as determined in the process of treatment planning. Metallic "seeds" placed within the tumor will be allowed to constitute a fiducial provided the methods are validated and a plan is in place to identify seed migration (e.g., redundant seeds placed).

##### 5.3.1.2 Dose Fractionation

Patients will receive 3 fractions of radiation. The dose for all patients will be 18 Gy per fraction to the prescription line at the edge of the PTV (total dose = 54 Gy). All treatment must be completed within 16 days. The time between fractions is at the discretion of the investigator, but a minimum of 40 hours and a maximum of 8 days should separate each treatment. **No more than 2 fractions will be delivered per week (7 consecutive days).**

##### 5.3.1.3 Premedications

Although not mandatory, it is recommended that patients receive corticosteroid premedication (e.g., Dexamethasone 4 mg p.o. in a single dose, or equivalent) 15-60 minutes before each of the three treatments for the intended purpose of modulating immediate pulmonary inflammatory effects. Analgesic premedication to avoid general discomfort during long treatment durations also is recommended when appropriate.

### 5.3.2 Technical Factors

#### 5.3.2.1 Physical Factors and Treatment Platforms

Only photon (x-ray) beams produced by linear accelerators with photon energies of 4-10 MV will be allowed. Cobalt-60 and charged particle beams (including electrons, protons, and heavier ions) are not allowed. Photon beam energies > 10 MV but < 15 MV will be allowed only for a limited number (≤ 50% of all beams or all beam angles) beams that must travel more than a cumulative distance of 10 cm through soft tissue (not lung) to reach the isocenter OR a shorter distance if the tumor abuts the chest wall (i.e., to spare skin dose).

Most commercially available photon producing treatment units are allowed except the exclusions noted above. As such, conventional linear accelerators, specialized linear accelerators with image guidance (e.g., Novalis, Trilogy, Synergy, Artiste) are allowed. These units can be used with conformal dose delivery or IMRT. Specialized dose painting accelerators (e.g., Cyberknife, or Tomotherapy) are allowed provided they meet the technical specifications of the protocol and are used in a fashion that passes the credentialing required by the protocol.

#### 5.3.2.2 Minimum Field Aperture (Field Size) Dimension)

Because of uncertainties in beam commissioning resulting from electronic disequilibrium within small beam apertures, an equivalent square field dimension of 3.0 cm is required for any field used for treatment delivery for sites using standard 3-D conformal techniques where nearly all of the PTV is encompassed for each beam. It is understood that this may exceed the technical requirements for small lesions [< 2.0 cm axial gross tumor volume (GTV) dimension or < 1.0 cm craniocaudal GTV dimension]. In such cases, the prescription dose is still prescribed to the edge of the defined planning treatment volume (PTV). For sites using dose painting including IMRT techniques (e.g., Cyberknife, Tomotherapy, etc.) where by design the entire PTV is not encompassed for each beam, smaller beam apertures are allowed.

#### 5.3.2.3 Dose Verification at Treatment

Personal dosimeter measurements (e.g., diode, TLD) may be obtained for surface dose verification for accessible beams as per institutional preference.

#### 5.3.2.4 The Use of Intensity Modulated Radiation Therapy (IMRT) Using Multileaf Collimation

The protocol allows for IMRT provided the site is credentialed for IMRT and SBRT. However, SBRT is, in general, a 3-D conformal treatment. Indeed, IMRT can result in dosimetric inaccuracies especially in circumstances where tumor motion is either unknown or not properly accounted. Some platforms inherently use IMRT and must pass credentialing where motion is incorporated correctly (e.g., Tomotherapy). When using other platforms, IMRT is generally discouraged. When required for successful compliance, IMRT should only be utilized if tumor motion is less than 5 mm, OR if motion management inherently diminishes motion effects (e.g., gating, breath hold, or tracking).

### 5.3.3 Localization, Simulation, and Immobilization

#### 5.3.3.1 Patient Positioning

Patients will be positioned in a stable position capable of allowing accurate reproducibility of the target position from treatment to treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be used, including stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients' external contours) with reference to the stereotactic coordinate system. Patient immobilization must be reliable enough to insure that the gross tumor volume (GTV) does not deviate beyond the confines of the planning treatment volume (PTV) with any significant probability (i.e., < 5%).

#### 5.3.3.2 Assessment of the Magnitude of Internal Organ Motion

Special considerations must be made to account for the effect of internal organ motion (e.g., breathing) on target positioning and reproducibility. As a first step, it is required that each site quantify the specific motion of a target so as to determine if management strategies listed in the next section are required to meet protocol guidelines. The GTV to PTV expansion limits, as defined below, are no greater than 0.5 cm in the axial plane and 1.0 cm in the craniocaudal plane. If tumor motion combined with set-up error causes the PTV to be greater than the GTV beyond these limits, then a motion management strategy (or plan to reduce setup

error) must be employed with validation of success. Patient should be instructed to be in normal free breathing at time of initial tumor motion assessment. Deep inspiration or expiration breath hold is not allowed for initial tumor motion assessment as such assessment generally overestimates free breathing tumor motion. Options for motion assessment included real time fluoroscopy, 4-D CT scanning, or other methods approved by the study team.

#### 5.3.3.3 Management of Effects of Internal Organ Motion

In some tumor locations, assessed tumor motion measurement indicates that tumor motion would exceed the required small tumor expansions per this protocol (resulting in marginal miss or excessive volume of irradiation) unless a motion management strategy is employed. Acceptable maneuvers for motion management include reliable abdominal compression, accelerator beam gating with the respiratory cycle, tumor tracking, and active breath-holding techniques or other methods approved by the study committee. Internal organ management maneuvers must be reliable enough to insure that the GTV does not deviate beyond the confines of the PTV with any significant probability (i.e., < 5%).

#### 5.3.3.4 Localization

Isocenter or reference point port localization films (anterior/posterior and lateral) should be obtained at each treatment on the treatment unit (or patients should undergo a tomographic imaging study using the linear accelerator couch, if available) immediately before treatment to ensure proper alignment of the geometric center (i.e., isocenter) of the simulated fields. All IGRT systems must be checked daily to guarantee coincidence between the imaging coordinate system and the treatment coordinate system. This test is required by the AAPM Task Group 142 report [130] and is described in detail in both the ASTRO/ACR practice guideline on SBRT available at:

http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/ro/stereo_body_radiation

and the ACR Technical Standard on IGRT available at:

http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/med_phys/monitor_IGRT.

This test is particularly important when the treatment equipment is not equipped with any device that allows direct visualization of anatomical structures using the treatment beam. For example, this test must be performed routinely for the CyberKnife, Tomotherapy units as well as any BrainLab equipment that does not include an electronic portal imaging device (EPID) that intercepts the treatment beam.

### 5.3.4 Treatment Planning/Target Volumes

#### 5.3.4.1 Image Acquisition

Computed tomography will be the primary image platform for targeting and treatment planning. The planning CT scans must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting and must be done with IV contrast unless the patient has allergic problems with contrast or has renal insufficiency. Contrast will allow better distinction between tumor and adjacent vessels or atelectasis. Axial acquisitions with gantry 0 degrees will be required with spacing ≤ 3.0 mm between scans. Images will be transferred to the treatment planning computers via direct lines, disc, or tape.

The target lesion will be outlined by an appropriately trained physician and designated the gross tumor volume. The target will generally be drawn using CT pulmonary windows; however, soft tissue windows with contrast may be used to avoid inclusion of adjacent vessels, atelectasis, or mediastinal or chest wall structures within the GTV. **This target will not be enlarged whatsoever for prophylactic treatment (including no "margin" for presumed microscopic extension); rather, include only abnormal CT signal consistent with gross tumor (i.e., the GTV and the clinical target volume [CTV] are identical)**. An additional 0.5 cm in the axial plane and 1.0 cm in the longitudinal plane (craniocaudal) will be added to the GTV to constitute the PTV.

As an alternative, sites equipped with 4-D CT scanning equipment may generate an Internal Target Volume (ITV) using the inspiration and expiration images or maximum intensity projections (MIP) as appropriate. Sites should be aware that the MIP reconstruction may erroneously define an ITV in cases of significant irregular breathing or when tumors abut soft tissue structures (e.g., the diaphragm). The 4-D scan acquired for planning, however, should be obtained after initial assessment of tumor motion confirming that the tumor motion will be no greater than 0.5 cm in the axial plane and 1.0 cm in the craniocaudal plane. In general, an

ITV should NOT be defined by the merger of a deep inspiration CT scan and a deep expiration CT scan as such would typically overestimate tumor motion. The ITV, then, is generated using a CT dataset where motion control maneuvers are already successfully employed. This ITV can be expanded by the institution's geometric set-up uncertainty (e.g., 4-5 mm) to generate the PTV.

As an example of this process, the University of Texas Southwestern employs the following steps to assess motion, manage motion, acquire image datasets, and generated targets. First a motion study is done (using fluoroscopy) to determine if the GTV is moving more than 1.0 cm. If it is, abdominal compression is applied with coaching (urging the patient not to "push back" against the abdominal plate) until the GTV moves less than 1.0 cm (verified again on fluoroscopy). Then, with compression/coaching applied when necessary, a 4-D CT is done. The 4-D CT allows the site to generate an ITV using either by a reconstructed MIP or with the expiratory/inspiratory phase scans, but this is a motion managed ITV (not necessarily free breathing). The site confirms that this motion managed ITV generated by the 4DCT (as opposed to the fluoroscopy assessment) has limited GTV motion per protocol requirements. As the site treats in a stereotactic body frame, the validated institutional setup error is small. The site compares the mid amplitude GTV expanded by 0.5-1.0 cm PTV as required by protocol requirements to the ITV plus setup error to insure they are consistent. The resulting PTV is small yet contains tumor motion and all of our setup errors.

**5.3.4.2 Dosimetry**

Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, non-coplanar beams are preferable. Typically, $\geq$ 10 beams of radiation will be used with roughly equal weighting. Generally, more beams are used for larger lesion sizes. When static beams are used, a minimum of seven non-opposing beams should be used. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized. For this protocol, when using a gantry mounted linear accelerator, the isocenter is defined as the common point of gantry and couch rotation for the treatment unit. For other types of treatment units (e.g., tomotherapy or CyberKnife), a reference point in space that is typically positioned at the center of the target is used instead of a mechanical isocenter. For non-IMRT or dose painting techniques, the conformal field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e., no additional "margin" for dose buildup at the edges of the blocks or MLC jaws beyond the PTV). The only exception will be when observing the minimum field dimension of 3 cm when treating small lesions (see above). As such, prescription lines covering the PTV will typically be the 60-90% line (rather than 95-100% as is common with conventional radiotherapy); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. The stereotactic reference point (corresponding to the mechanical isocenter for gantry mounted treatment units) will be determined from system fiducials (or directly from the tumor) and translated to the treatment record.

The treatment dose plan will be made up of multiple static beams or arcs as described above. For both IMRT and CyberKnife treatments, the apertures are determined by inverse treatment planning. In both cases, the end result is a very large number of beam apertures that do not necessarily include any particular single point in space. That is, the individual beams are not "isocentric." However, as stated above, whenever possible, IMRT plans should be avoided. The resulting plan should be initially normalized to a defined point corresponding closely to the center-of-mass of the PTV ($COM_{PTV}$). This normalization is used to select the isodose surface surrounding the target (see below where the exact coverage is stated as 95% of the PTV). Typically, in the case of the gantry mounted treatment units, this point will be the isocenter of the beam rotation; however, it is not a protocol requirement for this point to be the isocenter. For treatment units that do not have a mechanical isocenter, the center-of-mass of the PTV should be used. Regardless of the treatment unit type, the point identified as $COM_{PTV}$ must have defined stereotactic coordinates and must receive 100% of the normalized dose. Because the beam apertures for the 3D-CRT approach coincide nearly directly with the edge of the PTV (little or no added margin), the external border of the PTV will be covered by a lower isodose surface than usually used in conventional radiotherapy planning, typically around 80% but ranging from 60-90%. For the treatment techniques that use inverse planning algorithms, this same isodose coverage must be achieved. The prescription dose of 54 Gy in 3 fractions will be delivered to the margin of the PTV (as defined below) and fulfill the requirements below. As such, a "hotspot" will exist within the PTV centrally at the $COM_{PTV}$ with a magnitude of 54 Gy times the reciprocal of the chosen prescription isodose line (i.e., 60-90%).

**For purposes of dose planning and calculation of monitor units for actual treatment, approved corrections for tissue heterogeneity must be used.** Examples of appropriate tissue density heterogeneity correction algorithms include properly commissioned superposition/convolution (collapsed cone), AAA, and Monte Carlo. Simple pencil beam and Clarkson algorithms that account for attenuation but not scatter will not be allowed.

Successful treatment planning will require accomplishment of all of the following criteria:

1. **Normalization**

   The treatment plan should be normalized such that 100% corresponds to the center of mass of the PTV ($COM_{PTV}$). This point will typically also correspond (but is not required to correspond) to the isocenter of the treatment beams for gantry mounted devices.

2. **Prescription Isodose Surface Coverage**

   The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface of 54 Gy and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose (i.e., 48.6 Gy).

3. **Target Dose Heterogeneity**

   The prescription isodose surface selected in number 2 (above) must be ≥ 60% of the dose at the center of mass of the PTV ($COM_{PTV}$) and ≤ 90% of the dose at the center of mass of the PTV ($COM_{PTV}$). The $COM_{PTV}$ corresponds to the normalization point (100%) of the plan as noted in number 1 above.

4. **High Dose Spillage**

   a) Location: Any dose > 105% of the prescription dose should occur primarily within the PTV itself and not within the normal tissues outside the PTV. Therefore, the cumulative volume of all tissue outside the PTV receiving a dose > 105% of prescription dose should be no more than 15% of the size of the PTV volume.

   b) Volume: Conformality of PTV coverage will be judged such that the ratio of the volume of the prescription isodose meeting criteria 1 through 4 to the volume of the PTV is ideally < 1.2 (see table below). These criteria will not be required to be met in treating very small tumors (< 2.0 cm axial GTV dimension or < 1.0 cm craniocaudal GTV dimension) in which the required minimum field size of 3.0 cm results in the inability to meet a conformality ratio of 1.2.

5. **Intermediate Dose Spillage**

   The falloff gradient beyond the PTV extending into normal tissue structures must be rapid in all directions and meet the following criteria:

   a) Location: The maximum total dose over all 3 fractions in Gray (Gy) to any point 2 cm or greater away from the PTV in any direction must be no greater than $D_{2cm}$ where $D_{2cm}$ is given by the table below.

   b) Volume: The ratio of the volume of the 27 Gy isodose volume (50% of the prescription dose) to the volume of the PTV must be no greater than $R_{50\%}$ where $R_{50\%}$ is given by the table below.

6. **Adherence to Critical Organ Dose-Volume Limits**

**Acceptable Spillage Guidelines**

| Ratio of Prescription Isodose Volume to the PTV | | Ratio of 27 Gy Isodose Volume to the PTV, $R_{50\%}$ | | Maximum Dose at 2 cm from PTV in any direction as % of prescribed dose (PD). $D_{2cm}$ (Gy) = % x PD | | Percent of Lung receiving 20 Gy total or more, $V_{20}$ (%) | | PTV Volume (cc) |
|---|---|---|---|---|---|---|---|---|
| Deviation | | Deviation | | Deviation | | Deviation | | |
| none | acceptable | none | acceptable | none | acceptable | none | acceptable | |
| <1.2 | <1.5 | <5.9 | <7.5 | <50.0 | <57.0 | <10 | <15 | 1.8 |
| <1.2 | .<1.5 | <5.5 | <6.5 | <50.0 | <57.0 | <10 | <15 | 3.8 |
| <1.2 | <1.5 | <5.1 | <6.0 | <50.0 | <58.0 | <10 | <15 | 7.4 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| <1.2 | <1.5 | <4.7 | <5.8 | <50.0 | <58.0 | <10 | <15 | 13.2 |
| <1.2 | <1.5 | <4.5 | <5.5 | <54.0 | <63.0 | <10 | <15 | 22.0 |
| <1.2 | <1.5 | <4.3 | <5.3 | <58.0 | <68.0 | <10 | <15 | 34.0 |
| <1.2 | <1.5 | <4.0 | <5.0 | <62.0 | <77.0 | <10 | <15 | 50.0 |
| <1.2 | <1.5 | <3.5 | <4.8 | <66.0 | <86.0 | <10 | <15 | 70.0 |
| <1.2 | <1.5 | <3.3 | <4.4 | <70.0 | <89.0 | <10 | <15 | 95.0 |
| <1.2 | <1.5 | <3.1 | <4.0 | <73.0 | <91.0 | <10 | <15 | 126.0 |
| <1.2 | <1.5 | <2.9 | <3.7 | <77.0 | <94.0 | <10 | <15 | 163.0 |

Note 1: For values of PTV dimension or volume not specified, linear interpolation between table entries is required.

Note 2: Institutions are encouraged to stay within the values listed as "none" in the table above so that the treatment plan is considered to be per protocol. It is recognized that some treatment planning situations might be more challenging and fall outside these limits, so staying within the values listed as "acceptable" is also permitted. Protocol deviations greater than listed here as "acceptable" will be classified as "unacceptable" for protocol compliance.

### 5.3.5 Critical Structures

#### 5.3.5.1 Critical Organ Dose-Volume Limits

The following table lists dose limits to a point or volume within several critical organs/tissues. **For the spinal cord, these are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation**. For the non-spinal cord tissues, acceptable deviation allows a maximum point dose no more than 105% of the prescription dose (56.7 Gy as a total dose or 18.9 Gy per fraction) while fully respecting the defined volume constraint (for serial tissues) OR exceeding the parallel tissue critical volume dose maximum by no more than 5%. Unacceptable deviation exceeds the volume constraint for serial tissues, exceeds the maximum point dose for serial tissues by more than 105% of the prescription dose, or exceeds the parallel tissue critical volume dose maximum by more than 5%.

The normal tissue constraints listed in the following table list **total dose over 3 fractions** as well as per fraction. Participating centers are encouraged to observe prudent treatment planning principles in avoiding unnecessary radiation exposure to critical normal structures irrespective of these limits.

| **Serial Tissue** | **Volume** | **Volume Max (Gy)** | **Max Point Dose (Gy)**** | **Endpoint (≥ Grade 3)** |
|---|---|---|---|---|
| Spinal Cord and medulla | <0.35 cc<br><1.2 cc | 18 Gy (6 Gy/fx)<br>12.3 Gy (4.1 Gy/fx) | 21.9 Gy (7.3 Gy/fx) | Myelitis |
| Esophagus* | <5 cc | 17.7 Gy (5.9 Gy/fx) | 25.2 Gy (8.4 Gy/fx) | Stenosis/fistula |
| Brachial Plexus | <3 cc | 20.4 Gy (6.8 Gy/fx) | 24 Gy (8 Gy/fx) | Neuropathy |
| Heart/Pericardium | <15 cc | 24 Gy (8 Gy/fx) | 30 Gy (10 Gy/fx) | Pericarditis |
| Great vessels | <10 cc | 39 Gy (13 Gy/fx) | 45 Gy (15 Gy/fx) | Aneurysm |
| Trachea and Large Bronchus* | <4 cc | 15 Gy (5 Gy/fx) | 30 Gy (10 Gy/fx) | Stenosis/fistula |
| Rib | <1 cc | 28.8 Gy (9.6 Gy/fx) | 36.9 Gy (12.3 Gy/fx) | Pain or fracture |
| Skin | <10 cc | 30 Gy (10 Gy/fx) | 33 Gy (11 Gy/fx) | Ulceration |
| Stomach | <10 cc | 16.5 Gy (5.5 Gy/fx) | 22.2 Gy (7.4 Gy/fx) | Ulceration/fistula |
| Colon* | <20 cc | 24 Gy (8 Gy/fx) | 28.2 Gy (9.4 Gy/fx) | Colitis/fistula |
| **Parallel Tissue** | **Critical Volume** | **Critical Volume Dose Max (Gy)** | | **Endpoint (≥ Grade 3)** |
| Lung (Right & Left) | 1500 cc | 10.5 Gy (3.5 Gy/fx) | | Basic lung function |
| Lung (Right & Left) | 1000 cc | 11.4 Gy (3.8 Gy/fx) | | Pneumonitis |
| Liver | 700 cc | 17.1 Gy (5.7 Gy/fx) | | Basic liver function |
| Renal cortex (Right & Left) | 200 cc | 14.4 Gy (4.8 Gy/fx) | | Basic renal function |

* Avoid circumferential irradiation

** A "point" is defined as a volume of 0.035 cc or less

#### 5.3.5.2 Contouring of Normal Tissue Structures

**Spinal Cord**

The spinal cord will be contoured based on the bony limits of the spinal canal. The spinal cord should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV. **NOTE: For the spinal cord, these are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation.**

**Esophagus**

The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The esophagus should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV.

**Brachial Plexus**

The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neuroforamina on the involved side from around C5 to T2. However, for the purposes of this protocol, only the major trunks of the brachial plexus will be contoured. The brachial plexus will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the second rib. If the PTV is more than 10 cm away from the brachial plexus, this structure need not be contoured.

**Heart**

The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aorto-pulmonary window) and extend inferiorly to the apex of the heart.

**Trachea and Proximal Bronchial Tree**

The trachea and proximal bronchial tree will be contoured as two separate structures using mediastinal windows on CT to correspond to the mucosal, submucosa and cartilage rings and airway channels associated with these structures. For this purpose, the trachea will be divided into two sections: the proximal trachea and the distal 2 cm of trachea. The proximal trachea will be contoured as one structure, and the distal 2 cm of trachea will be included in the structure identified as proximal bronchial tree. Differentiating these structures in this fashion will facilitate the eligibility requirement for excluding patients with tumors within 2 cm of the proximal bronchial tree.

**Proximal Trachea**

Contouring of the proximal trachea should begin at least 10 cm superior to the extent of the PTV or 5 cm superior to the carina (whichever is more superior) and continue inferiorly to the superior aspect of the proximal bronchial tree.

**Proximal Bronchial Tree**

The proximal bronchial tree will include the most inferior 2 cm of distal trachea and the proximal airways on both sides as indicated in the diagram in above. The following airways will be included according to standard anatomic relationships: the distal 2 cm of trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus, and the right and left lower lobe bronchi. Contouring of the lobar bronchi will end immediately at the site of a segmental bifurcation.

**Whole Lung**

Both the right and left lungs should be contoured as one structure. Contouring should be carried out using pulmonary windows. All inflated and collapsed lung should be contoured; however, gross tumor (GTV) and trachea/ipsilateral bronchus as defined above should not be included in this structure.

**PTV + 2 cm**

As part of the QA requirements for "low dose spillage" listed above, a maximum dose to any point 2 cm away in any direction is to be determined. To facilitate this QA requirement, an artificial structure 2 cm larger in all directions from the PTV is required. Most treatment planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning. If possible this structure should be constructed as a single contour that is 2 cm larger than the PTV.

**Proximal Bronchial Tree + 2 cm**

As part of adhering to the ineligibility requirements for not enrolling patients with tumors in the zone of the proximal bronchial tree depicted above, it is convenient to define an artificial structure 2 cm larger in all directions from the proximal bronchial tree. If the GTV falls within this artificial structure, the patient should not be treated with the protocol therapy.

**Skin**

The skin will be defined as the outer 0.5 cm of the body surface. As such it is a rind of uniform thickness (0.5 cm) which envelopes the entire body in the axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations (e.g., the scalp on the top of the head).

**Rib**

Ribs within 5 cm of the PTV should be contoured by outlining the bone and marrow. Typically, several portions of adjacent ribs will be contoured as one structure. Adjacent ribs, however, should not be contoured in a contiguous fashion (i.e., do not include the inter-costal space as part of the ribs).

**Other Structures**

The constraints tables above contain other structures. These are required if the structure is within 10 cm of the PTV.

### 5.3.6 Planning Priorities

Successful treatment planning goals are listed above. In general, attempts should be made to successfully satisfy all of the goals without deviation. In some circumstances, improvements can be made to the dosimetry plan beyond simply meeting the specified goals. In other circumstances, clinicians are faced with the prospect of not ideally meeting one or more of the goals (i.e., accepting an acceptable deviation). In this section, we provide priorities in which a most ideal plan for protocol purposes is realized. Suggested priority of planning goals in order of importance is:

1. Respect spinal cord dose constraints.
2. Meet dose "compactness" constraints including the high dose conformality constraint, D2cm, and R50
3. Meet organ constraints other than spinal cord.

The organ constraints are last in priority (except for spinal cord tolerance), because they are the least validated. The "essence" of a stereotactic plan is captured mostly in the dose compactness justifying their higher priority. As an example in a case where not all goals can be met, it would be suggested to meet dose compactness goals without deviation even at the expense of a non-spinal cord normal tissue having acceptable deviation. Unacceptable deviations should be avoided in all cases. Again, these are suggested planning priorities and clinicians must use there judgment and experience in actual treatment given the variability of patient presentation and tolerance.

As an example, in some cases a target abuts a normal tissue structure with an assigned constraint. Obviously, it would be impossible to utilize the required expansions, treat to 54 Gy PTV dose, and also meet the normal tissues maximum dose constraint. With the exception of the spinal cord, the protocol allows an "acceptable" deviation such that the abutting normal tissue is allowed a maximum point dose of 105% of the prescription dose; however, the volume constraint must still be respected. As such, the dosimetry might be manipulated by falloff dose polarization so that the compactness criteria are met with an "acceptable" deviation of normal tissue constraints.

### 5.3.7 Treatment Interruptions and Adverse Event Management Guidelines

In general, the need for treatment interruptions is rare in patients receiving SBRT. Interruptions should be avoided by preventative medical measures and nutritional, psychological, and emotional counseling. Treatment breaks, including indications, must be clearly documented in the treatment record.

**Pneumonitis**

Radiation pneumonitis is a subacute (weeks to months from treatment) inflammation of the end bronchioles and alveoli. **Note:** It is very important that a Radiation Oncologist participate in the care of the patient, as the clinical picture may be very similar to acute bacterial pneumonia, with fatigue, fever, shortness of breath, nonproductive cough, and a pulmonary infiltrate on chest x-ray. The infiltrate on chest x-ray should include the area treated to high dose, but may extend outside of these regions. The infiltrates may be characteristically "geometric" corresponding to the radiation portal, but may also be ill defined.

Patients reporting symptoms as above will be promptly evaluated and treated. Mild radiation pneumonitis may be treated with nonsteroidal anti-inflammatory agents or steroid inhalers. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary toilet. Supra- and concurrent infections should be treated with antibiotics. Consideration of prophylaxis of opportunistic infections should be considered in immunocompromised patients.

It is unlikely that symptomatic pneumonitis will occur during the weeks radiation is actually delivered to the patients. However, if a patient experiences pneumonitis before completing therapy, therapy will be put on hold until symptoms resolve.

When symptomatic pneumonitis resolves to grade 0, the treating physician will contact the RTOG Study Co-chair for a decision to continue or terminate protocol therapy. All decisions by the RTOG Co-chair must be documented in the patient's chart.

**Bronchial Injury (e.g., bronchial obstruction; bronchial stricture; bronchopleural fistula)**

Bronchial injury with subsequent focal collapse of lung may impair overall pulmonary status. It also makes further assessment of tumor response more difficult as the collapsed lung approximates the treated tumor. Because atelectatic lung and tumor have similar imaging characteristics, radiology reports will often describe the overall process as progressive disease while the actual tumor may be stable or shrinking. Investigators are referred to the strict criteria for progressive disease to avoid such mischaracterization.

The consequences of bronchial toxicity, e.g., cough, dyspnea, hypoxia, impairment of pulmonary function test parameters, pleural effusion or pleuritic pain (associated with collapse), will all be graded and reported on adverse event forms.

**Chest Wall Pain and/or Fracture (Rib)**

When treating lesions about the chest wall, some patients will experience chest wall pain either as a result of intercostal neuropathy or rib fracture. Focal radiation induced osteoporosis can result in both occult and obvious rib fractures generally propagated by severe coughing/sneezing episodes or chest wall trauma (e.g., bumping into a kitchen cabinet). The pain typically occurs several months after treatment and may last several more months.

**Changes in Pulmonary Function Tests (e.g., forced expiratory volume (FEV1) decreased; carbon monoxide diffusion capacity (DLCO) decreased; vital capacity abnormal)**

Patients enrolled to this study may have some degree of impaired pulmonary function as measured by pulmonary function tests (PFTs), including Forced Expiratory Volume in 1 second ($FEV_1$), Forced Vital Capacity (FVC), and Diffusing Capacity for Carbon Monoxide (DLCO). The CTCAE Version 4 grading criteria for PFTs assume that all patients have normal baseline pulmonary function. This assumption is not appropriate for this protocol, which is enrolling patients with abnormal baseline function. In order to monitor changes in lung function from baseline, a protocol-specific toxicity classification for PFTs has been developed for use with this study. PFTs will be coded for all patients in both treatment groups using this scale. See RTOG Pulmonary Function Test Toxicity Scale (Section 8.4) for more information.

**Other Grade 3 or Higher Adverse Events**

All other adverse events Grade 3 or higher, or requiring suspension of therapy, will be reported.

#### 5.3.8 Compliance Criteria

##### 5.3.8.1 Credentialing Compliance

All criteria listed in Credentialing (Section 12) must be completed to the satisfaction of the study team in order to participate in the study. No institution will be allowed to enroll patients without completion of all required credentialing.

##### 5.3.8.2 Dosimetry Compliance

The Image-Guided Therapy Center (ITC) will evaluate dosimetry plans (see Quality Assurance Requirements, Section 5.4). RT treatment plans not meeting the "per protocol" criteria or scored as "variation acceptable" will be classified as "deviation unacceptable." Normal tissue dose constraints are listed above. **NOTE: For the spinal cord, these are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation.** For the non-spinal cord tissues, acceptable deviation allows a maximum point dose no more than 105% of the prescription dose (56.7 Gy or 18.9 Gy per fraction) while fully respecting the defined volume constraint (for serial tissues) OR exceeding the parallel tissue critical volume dose maximum by no more than 5%. Unacceptable deviation exceeds the volume constraint for serial tissues, exceeds the maximum point dose for serial tissues by more than 105% of the prescription dose, or exceeds the parallel tissue critical volume dose maximum by more than 5%.

##### 5.3.8.3 Contouring Compliance

Accurate and appropriate contouring is essential for the generation of dose volume statistics. In addition, it is the desire of ACOSOG and RTOG to compile a comprehensive database of dose volume information coupled with outcomes data (control/toxicity) in order to define accurate dose response effects. As such, we require that the tumor targets, lungs, esophagus, bronchial tree, spinal cord, heart (pericardium), and trachea be contoured in all patients. In addition, any structure listed with a constraint in Critical Structures and residing within 10 cm in any direction from the PTV must be contoured. Appropriateness of contouring will be scored by the study PIs as either no deviation, minor deviation, or major deviation.

#### 5.3.9 SBRT Quality Assurance Documentation

See Quality Assurance Requirements (Section 5.4).

## 5.4 Quality Assurance Requirements

Surgical quality assurance will be performed by the study chair or designee, as specified below. Brachytherapy and SBRT quality assurance (and credentialing – see Section 12) will be conducted by the Advanced Technology Consortium (ATC), which is a "virtual entity" made up of the following QA centers:

- Image-guided Therapy QA Center (ITC), Washington University in St. Louis
- Radiation Therapy Oncology Group (RTOG) Headquarters Dosimetry Group
- Radiological Physics Center (RPC), M.D. Anderson Cancer Center
- Quality Assurance Review Center (QARC), Lincoln, RI.

#### 5.4.1 Surgery Quality Assurance

All operative and pathology reports will be reviewed by the surgical study chair or designee for success of the resection, as defined in Section 5.1. Problems or concerns about investigator performance will be communicated directly to the investigator by the study chair.

#### 5.4.2 Brachytherapy Quality Assurance

Brachytherapy quality assurance documentation and imaging will be submitted to the Image-guided Therapy QA Center (ITC).

Within two weeks after completion of the post-implant CT scan, submit the following for each patient receiving brachytherapy:

- Baseline diagnostic PET/CT scan (DICOM) of the chest
- Post-implant CT scan (DICOM) at 4 weeks used for treatment planning

- Structure contours (DICOM RT Structure Set) for all structures identified in section 5.2.4
- 3-D CALCULATED dose distributions (DICOM RT Dose) throughout the volume of interest
- Treatment plan information (DICOM RT treatment plan)
- Color isodose images in axial, sagittal, and coronal planes (JPEG or PNG screen captures)
- Color DVH's for the resection margin, 0.5 cm depth (PTV-1), 0.7 cm depth (PTV-2), 1.0 cm depth, and 2.0 cm depth (JPEG or PNG screen captures)
- Online Digital Data Submission Information (DDSI) Form (available at http://atc.wustl.edu/forms/DDSI/ddsi.html - username and password required) to report the specified dose parameters (activity/seed, total seeds/strands, total activity, measured strand separation). NOTE: This on-line form will accompany all submissions to ITC.

The required imaging must be submitted digitally in DICOM format. The DICOM files must have the ability to be extracted from the CD. Submission by either CD or SFTP is supported. See QA Submission Instructions (Section 5.4.4).

### 5.4.3 SBRT Quality Assurance

SBRT quality assurance documentation and imaging also will be submitted to ITC for review.

#### 5.4.3.1 Rapid Review of Treatment Plan for First Patient

Rapid review of the first patient's treatment plan prior to treatment is required for each type of SBRT system used at a site (e.g., Cyberknife, Linac-based, etc.).

The rapid review allows the study team to determine the institution's ability to generate a "per protocol" treatment plan. Each institution must digitally submit the planning CT dataset with the proposed treatment plan prior to the start of treatment for the first patient registered by the institution. The plan will be reviewed centrally by the study co-chair or designee, and suggestions regarding protocol compliance will be forwarded to the participating institution. Once the plan is approved, RTOG Headquarters will notify the site, and treatment may begin.

Prior to the start of SBRT, submit the following materials for the first patient treated with each type of SBRT system used at a site:

- Planning CT dataset (DICOM)
- Structure contours (DICOM RT Structure Set) for critical normal structures, all GTV, CTV, and PTV contours (C1, C3)
- Treatment plan (DICOM RT Plan) for initial and boost beam sets
- 3-D CALCULATED dose distributions (DICOM RT Dose) for initial and boost sets of concurrently treated beams
- Color isodose images in axial, sagittal, and coronal planes (JPEG or PNG screen captures)
- Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan (DV)
- Online Digital Data Submission Information Form (DDSI) (available at http://atc.wustl.edu/forms/ddsi/ddsi.html).

The required imaging must be submitted digitally as DICOM RT. Submission by either CD or SFTP is supported. See QA Submission Instructions (Section 5.4.4).

#### 5.4.3.2 Treatment Plan Review for Subsequent Patients

Only the first patient's treatment plan for each system used at each site will be reviewed prior to treatment. For all subsequent patients, the study co-chair or designee will perform retrospective treatment plan review after complete data for the first 50 cases enrolled have been received at ITC. Subsequent reviews will be performed for every 50 patients enrolled and treated with SBRT thereafter.

**Required Materials for Subsequent Patients**

Within four weeks after completion of SBRT, submit the required materials identified in Section 5.4.3.1 for all patients.

The required imaging must be submitted digitally as DICOM RT. Submission by either CD or SFTP is supported. See QA Submission Instructions (Section 5.4.4).

#### 5.4.3.3 Final Dosimetry Data Submission for All Patients

Within four weeks after completion of SBRT, submit hard copies of the following for all patients:

- Radiotherapy Form (T1) (available on the Z4099 page of http://www.acosog.org)
- Daily radiation treatment record from patient's medical chart

Hard copies of the T1 form and treatment records will be submitted to ITC. See QA Submission Instructions (Section 5.4.4).

### 5.4.4 QA Submission Instructions

All CT planning and treatment information (e.g., post-implant CT files, dose files, plan files, and structure files) must be submitted digitally in DICOM RT format. Submission by either CD or SFTP is supported. Multiple studies for the same patient may be submitted on one CD; however, submit only one patient per CD.

All submissions via CD or hard copy should be sent to:

Image-guided Therapy QA Center

4511 Forest Park Ave, Suite 200

St. Louis, MO 63108

Phone: (314) 747-5415

Fax: (314) 747-5423

Email: itc@wustl.edu

A Secure FTP (SFTP) account with username and password can be obtained by contacting the ITC at (314) 747-5415 or itc@wustl.edu. Guidelines for digital submission are available at http://atc.wustl.edu.

Sites must notify ITC via e-mail when digital data are submitted. The e-mail must include the study and patient identification numbers and a description of the datasets being submitted (e.g., brachytherapy QA, SBRT treatment plan, etc.).

**NOTE: If brachytherapy or SBRT data cannot be submitted, the ITC must be notified. The notification must be submitted in writing via email to itc@wustl.edu.**

## 5.5 Systemic Therapy

Patients with clinical or pathological Stage Ia or Ib should not be offered chemotherapy, as eligible patients per staging should have tumors ≤ 3 cm.

Patients found at surgery to have pathological Stages Ib (> 3 cm), IIa, IIb and IIIa may be offered adjuvant chemotherapy at the discretion of the treating physician.

The regimen chosen will be at the discretion of the treating physician. Any adjuvant chemotherapy administered to the patient must be documented in the patient's hospital/clinic chart.

## 5.6 Early Discontinuation of Protocol Therapy

Protocol therapy may be discontinued early at the discretion of the investigator for the following reasons:

- Excessive or unacceptable toxicity
- Patient refusal or withdrawal of consent for treatment
- Disease relapse/progression during therapy

Patients who discontinue treatment early should be followed as described in Follow-up (Section 6).

# 6 Follow-up

After completion of protocol therapy, patients will be monitored for relapse/progression and survival for five years as required by the Study Calendar.

## 6.1 Follow-up of Patients Who Do Not Receive Protocol Treatment

Registered patients who do not receive protocol therapy will be followed as required by the Study Calendar.

## 6.2 Follow-up of Patients with Disease Relapse/Progression

Patients with local, regional or distant disease relapse/progression during or after protocol therapy will be followed for survival and quality of life, as required by the Study Calendar. Patients may be treated at the physician's discretion. NOTE: If resection is attempted after disease relapse/progression, submit operative and pathology reports and 4-week post-surgery adverse event data.

## 6.3 Follow-up of Patients Who Discontinue Treatment Early for Reasons Other Than Disease Relapse/Progression

Patients who discontinue protocol therapy for reasons other than disease relapse/progression will be followed as required by the Study Calendar.

# 7 Evaluation of Outcomes

All patients will be followed for 5 years for survival and disease relapse/progression. Adverse events including surgical morbidity and mortality and late radiation effects also will be monitored. Quality of life will be evaluated for patients who have consented to participate in that portion of the study.

## 7.1 Response to SBRT (Arm 2)

Response to SBRT will be assessed and reported according to RECIST Version 1.1 criteria.

**Evaluation of Target Lesions (Primary Tumor)**

- **Complete Response (CR)**: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- **Partial Response (PR)**: At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD)**: At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- **Stable Disease (SD)**: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

## 7.2 Relapse/Progression Definitions

All patients will be assessed for disease relapse/progression. The types of local, regional and distant relapse/progression will be recorded to determine if there are differences in the pattern of relapse/progression between arms.

PET/CT is required to confirm disease relapse/progression (i.e., if CT scan alone is suspicious for relapse/progression, then PET/CT is required to confirm disease status). Biopsy confirmation of relapse is highly recommended but not required. When biopsy is feasible, the following methods are recommended: fine-needle aspiration biopsy, EBUS, EUS, VATS or open biopsy.

CT imaging at three months will be considered the new baseline to account for inflammatory changes and fibrosis after SBRT or SR. The table below describes the different areas defined as local, regional, and distant relapse/progression after treatment effects have subsided.

**Categories of Relapse/Progression**

| Type of Recurrence | Modality | Description (after treatment effects have subsided) |
|---|---|---|
| **Local Failure** | | |
| Primary tumor failure (PTF) | SBRT | Appearance of residual tumor located within the extent of the primary targeted tumor. |
| Marginal failure (MF) | SR/SBRT | SR: Appearance of tumor $\leq$ 2 cm in any direction of the staple-line or the structures immediately adjacent to prior tumor site (chest wall/ mediastinum/ diaphragm/ spine).<br>SBRT: Appearance of tumor $\leq$ 2 cm in any direction of the primary tumor or structures immediately adjacent to primary tumor (lung/ chest wall, mediastinum/ diaphragm/ spine). |
| Involved Lobe failure (ILF) | SR/SBRT | SR: Appearance of tumor > 2 cm in any direction of the staple-line.<br>SBRT: Appearance of tumor > 2 cm in any direction of the primary tumor. |
| Port site/wound failure (PWF) | SR | Appearance of tumor at a port or incision site after VATS or open resection. |
| **Regional Failure** | | |
| Non-primary lobe failure (NLF) | SR/SBRT | Appearance of tumor within another ipsilateral (non-primary) lobe. |
| Hilar nodal failure (HNF) | SR/SBRT | Appearance of tumor in ipsilateral hilar lymph nodes |
| Ipsilateral mediastinal nodal failure (MNF) | SR/SBRT | Appearance of tumor in ipsilateral mediastinal and/or subcarinal lymph nodes. |
| **Distant Failure** | | |
| Distant nodal failure (DNF) | SR/SBRT | Appearance of tumor in ipsilateral supraclavicular or contralateral lymph nodes . |
| Distant metastatic failure (DMF) | SR/SBRT | Appearance of tumor deposits characteristic of NSCLC metatstasis (chest wall other than incision sites or immediately adjacent to primary, mediastinal structures/diaphragm, malignant pleural effusion/pericarial effusion), contralateral lung and/or other distant sites. |

## 7.3 Documentation of Relapse/Progression

Submission of the biopsy pathology report (if available) and scan reports at the time of relapse/progression is required for all patients. See the Schedule of Forms.

### 7.3.1 Central Review of Imaging at Relapse/Progression

Submission of imaging to document disease relapse/progression is required in the absence of a tissue diagnosis. Imaging also may be requested by the study team for confirmation of reported relapse/progression on a case-by-case basis. Within 1 month after the request is received by the site, electronic copies of the imaging should be sent to the ITC. The following imaging and reports are required:

- Images from the CT scan done at 3 months post-treatment
- Images from the CT scan and PET/CT scan done at the time of relapse/progression
- Copies of the corresponding radiology reports
- Online Digital Data Submission Information Form (DDSI) (available at http://atc.wustl.edu/forms/ddsi/ddsi.html).

All materials must be submitted to:

Image-guided Therapy QA Center

4511 Forest Park Ave, Suite 200

St. Louis, MO 63108

Phone: (314) 747-5415

Fax: (314) 747-5423

Email: itc@wustl.edu

The retrospective central review may be conducted electronically via the internet, so imaging must be submitted digitally in DICOM format. The digital files may be burned to a CD and mailed to ITC. Multiple studies for the same patient may be submitted on one CD; however, submit only one patient per CD. Alternative electronic methods (e.g., sFTP) are possible. Contact ITC for more information.

# 8 Adverse Event Reporting

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Toxicities/adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Toxicity Criteria (CTCAE), Version 4.0 (except changes in PFTs – see Section 8.4). The CTCAE is available at http://ctep.cancer.gov/reporting/ctc.html. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided.

## 8.1 Routine Adverse Event Reporting

All expected or unexpected adverse events, regardless of grade or treatment attribution, must be recorded on AE case report forms (CRFs).

Some serious adverse events may require expedited reporting using the AdEERS reporting system, as defined below. **NOTE: All AEs including those submitted to NCI via the Adverse Event Expedited Reporting System (AdEERS) must be recorded on the AE CRF.** Expedited reporting is in addition to and does not supplant the reporting of AEs as part of the data submission requirements for the study.

## 8.2 Expedited Adverse Event Reporting

An expedited AE report is submitted via the AdEERS web application. Assistance for using AdEERS or for completion of the AdEERS templates is available at http://ctep.cancer.gov/.

**What to Report**

**AdEERS Reporting Requirements for Adverse Events that Occur within 30 Days[1] of the End Date of Non-investigational Treatment on Phase III Trials**

| | Phase III Trials | | | | | | |
|---|---|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | | Grade 5 | |
| | Unexpected and Expected | Unexpected and Expected | Unexpected and Expected | Unexpected | Expected | Unexpected | Expected |
| **Unrelated Unlikely** | Not Required | Not Required | Not Required | Not Required | Not Required | 10 Calendar Days | 10 Calendar Days |
| **Possible Probable Definite** | Not Required | Not Required | Not Required | 10 Calendar Days | Not Required | 10 Calendar Days | 10 Calendar Days |

1 **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment (surgery or radiation) require reporting as follows:**

AdEERS 10 calendar day report:

- Grade 4 and Grade 5 unexpected events

**How to Report**

AdEERS reports are submitted electronically via the AdEERS web application.

The AdEERS application is available at: http://ctep.cancer.gov/reporting/adeers.html.

**Where to Report**

For electronic submission: Use the AdEERS web application.

**Secondary Malignancies**

All cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) that occur in patients on NCI-sponsored trials following treatment for cancer will be reported via the AdEERS web application within 30 days of an AML/MDS diagnosis.

**IRB Submission**

All local AdEERS reports must be submitted to your Institutional Review Board (IRB) within 90 days of knowledge and reporting of the event. You should follow your IRB's policies and procedures in submitting external adverse events and safety reports.

## 8.3 Expected Adverse Events

### 8.3.1 Surgery

Atelectasis, lung infection, pneumonitis, dyspnea, adult respiratory distress syndrome, pleural infection, thromboembolic event, myocardial infarction, ventricular arrhythmia, arterial injury, venous injury, wound infection, bronchopleural fistula, postoperative hemorrhage, sepsis, recurrent laryngeal nerve palsy, intraoperative respiratory injury, postoperative thoracic procedure complication, changes in pulmonary function tests (e.g., forced expiratory volume (FEV1) decreased; carbon monoxide diffusion capacity (DLCO) decreased; vital capacity abnormal).

### 8.3.2 Brachytherapy

Lung infection, pneumonitis, dyspnea, adult respiratory distress syndrome, pleural infection, bronchopleural fistula.

### 8.3.3 Z4032 Adverse Event Data

In addition to the risks listed above, the most common (i.e., occurring in four or more instances) Grade 3 or higher events identified in the Z4032 SR and SR + BR arms include (in CTCAE V3 terms): hemorrhage – surgical, infection (pneumonia) with Grade 0-2 ANC, infection (pneumonia) with unknown ANC, urinary tract infection, hypoxia, atrial fibrillation, hypotension, dehydration.

### 8.3.4 Stereotactic Body Radiation Therapy

Pneumonitis, atelectasis, bronchial obstruction, bronchial stricture, bronchopleural fistula, chest wall pain, fracture, changes in pulmonary function tests (e.g., forced expiratory volume (FEV1) decreased; carbon monoxide diffusion capacity (DLCO) decreased; vital capacity abnormal), pulmonary fibrosis, burn, dermatitis radiation, alopecia, cough (may be productive), dyspnea, fever, fatigue, pericarditis, pericardial effusion, chest pain – cardiac, palpitations, heart failure, myocardial infarction, paresthesias, generalized muscle weakness, esophagitis, dysphagia, aortic or arterial injury, hemoptysis, pain of skin.

## 8.4 RTOG Pulmonary Function Test Toxicity Scale

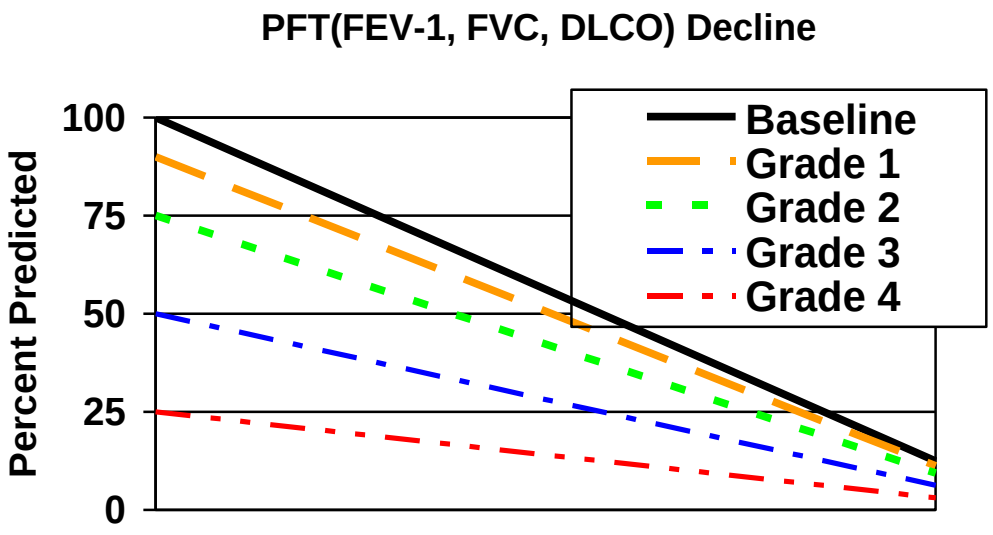
Changes in pulmonary function tests (FEV-1, FVC, DLCO, etc) for all patients will be graded using the RTOG Pulmonary Function Test Toxicity Scale. The RTOG Pulmonary Function Test Toxicity Scale is preferred for this protocol because it accounts for baseline abnormalities in pulmonary function which will be common based on the protocol's eligibility criteria.

Changes that occur after therapy will be referenced to baseline for a given patient, which will be abnormal for most patients. The RTOG scale defines a proportional decline from the baseline. Grade 1 toxicity will be a decline from baseline to a level 0.90 times the baseline, grade 2 will be a decline to a level 0.75 of baseline, grade 3 will be a decline to a level 0.5 of baseline, grade 4 will be a decline to a level 0.25 of baseline, and grade 5 will be death. This scheme is depicted in the table below and graphically represented

in the figure below. Both arms of this trial will utilize this alternate pulmonary function toxicity scale rather than the CTCAE for grading and reporting changes in PFTs.

As an example, a patient who enters the study with a percent predicted DLCO of 55% who experiences a post treatment decline to a percent predicted DLCO of 40% would have a grade 4 event in the original CTCAE version 4 criteria; however, under this modified PFT toxicity classification for patients with abnormal baseline, his decline would constitute a decrease to 0.72 of the baseline value which is between 0.75 and 0.5 or a grade 2 event.

| RTOG Pulmonary Function Test Toxicity Scale | | | | | |
|---|---|---|---|---|---|
| | Grade | | | | |
| Adverse Event | 1 | 2 | 3 | 4 | 5 |
| FEV-1 Decline | 0.90-0.75 times the patient's baseline value | <0.75-0.50 times the patient's baseline value | <0.50-0.25 times the patient's baseline value | <0.25 times the patient's baseline value | Death |
| Forced Vital Capacity Decline | 0.90-0.75 times the patient's baseline value | <0.75-0.50 times the patient's baseline value | <0.50-0.25 times the patient's baseline value | <0.25 times the patient's baseline value | Death |
| DLCO Decline | 0.90-0.75 times the patient's baseline value | <0.75-0.50 times the patient's baseline value | <0.50-0.25 times the patient's baseline value | <0.25 times the patient's baseline value | Death |



# 9 Data Considerations

All CRFs are available on the Z4099 page of the ACOSOG web site at http://www.acosog.org or under the Protocols tab of the CTSU website at https://www.ctsu.org.

## 9.1 Case Report Form Completion and Submission Guidelines

This study will utilize Medidata Rave® for remote data capture (RDC) of all data.

To receive Rave system access, sites must complete the ACOSOG Roster Personnel Information Form (available at https://ncctg.mayo.edu/acosog/roster-rdc-access.dot) and fax the completed form to the number provided. The ACOSOG Roster Personnel Form is required for each person responsible for data entry and should be submitted prior to the first patient registration.

Allied Health Professionals/CRAs at participating sites will receive two emails: 1) an email invitation from iMedidata-Notification@mdsol.com to set up their user id and password; and 2) an email which provides additional instructions on account setup. Once an account is established, eLearning modules will be provided for Rave RDC instruction. All modules must be completed prior to gaining access to data entry. Further training opportunities will be communicated through the web site.

The Rave system can be accessed through the iMedidata portal at https://login.imedidata.com.

Contact the QA Specialist with all questions about Medidata Rave.

# 10 Statistical Considerations

## 10.1 Study Design

This is a randomized Phase III non-inferiority trial design comparing the control arm, sublobar resection (SR) with or without brachytherapy, to the experimental arm, stereotactic body radiation (SBRT) in operably high-risk patients with stage I non-small cell lung cancer (NSCLC).

### 10.1.1 Primary Endpoint

The primary aim of this Phase III trial is to test the hypothesis that SBRT for operable high-risk patients with stage I NSCLC is not inferior to SR with or without brachytherapy. The primary endpoint is overall survival defined as the time from randomization until death from any cause. All patients will be followed for the primary endpoint for a minimum of 5 years..

Based on historical data, we expect the three-year survival rate for SR (control group) to be 80%. We will accept a 10% decrement from the three-year survival rate for SR arm of the study to be considered non-inferior. Rationale for the up to 10% decrement in three-year survival for the SBRT arm is that SBRT is expected to be significantly better tolerated (i.e. have a significantly better adverse event profile) than SR. One line of evidence to support this expectation is that it has been established that stage I patients who are medically inoperable (unable to tolerate any form of lung resection) can tolerate SBRT because it is less invasive and has a lower adverse event profile compared to SR. Hence, in this high-risk population (patient who can tolerate SR but not the first line surgery of lobar resection), SBRT will likely have a considerably better adverse event profile (and QOL profile) than SR. There is also some evidence in the literature that supports a significantly improved adverse event profile of SBRT compared to SR in this population. Specifically, a large study of 182 patients undergoing segmental resection demonstrated complications in 32.4% of patients [103]. This compares to a recent report of SBRT that reported a 10% rate of grade 3+ toxicities [19]. It is difficult to compare these values because they did not use the same adverse event grading scale. However, this potentially indicates that the expected grade 3+ adverse event rate for SRBT might be half that for SR. Given this, it is felt that an inferiority margin of at most 10% in three year survival is balanced by a anticipated decrease in grade 3+ adverse events of a substantial amount (potentially 50% or more) in SBRT compared to SR.

### 10.1.2 Secondary Endpoints

The secondary objective of this Phase III trial is to compare the time-to-locoregional recurrence using a standardized definition of locoregional recurrence to be applied to both arms. In brief, locoregional

recurrence will be defined as recurrence within the same lobe or hilum (N1 nodes), or within 2 cm of the staple line or within 2 cm of the PTV after treatment effects such as scarring have subsided. This will be a first attempt to set comparable locoregional recurrence definitions for these two different treatment modalities.

Other secondary endpoints are adverse events, disease-free survival, and pulmonary function. Adverse event rates will be compared at specific timepoints (1, 3, and 12 months post therapy). Disease-free survival is defined as the time from randomization until documented disease-recurrence or death, whichever occurs first. Patient who are disease-free and alive at the time of analysis will be censored at the time of their last follow-up. Patients will be followed for disease-free survival for a minimum of 5 years. Pulmonary function will be evaluated by PFTs and will be compared at specific timepoints as well as over the entire period of observation.

A tertiary aim of the study is to compare the adverse event rates and PFT values in each arm for patients with low or high Charlson comorbidity index scores, including a test interaction between Charlson Comorbidity Index scores (low vs. high) and treatment arm. If there a substantial interaction term, this index may potentially be used to select patients for SBRT or SR.

## 10.2 Sample Size

This is a non-inferiority trial designed to determine whether the overall survival rate for SBRT is clinically (and statistically significantly) no worse than the overall survival for SR. We used published survival rates from the literature for SR in this patient population [2, 8, 19, 103]. The 3-year survival rate for SR (control group) appears to be approximately 80%. We will deem SBRT as non-inferior to SR if the 3 year overall survival rate for SBRT is no more than 0.10 less than that for SR. In other words, if the survival rate for SBRT at 3 years is more than 0.10 less than the 3 year survival rate for SR, we will declare SBRT to be an inferior treatment compared to SR in terms of overall survival. To power the study, we assumed an exponential distribution for the survival rate and a HR of 1.60 (which reflects a 10% 3-year survival difference). The null hypothesis is that the HR is 1.60 (SBRT versus SR), which implies the 3-year survival rate for SR is at least 0.10 greater than that for SBRT (0.80 for SR versus 0.70, or less, for SBRT). The alternative hypothesis is that the HR is 1.00 or that the 3 year survival rate for the SBRT is no worse than that for SR, defined as the difference in the 3 year survival rate for SR compared to SBRT is no more than 0.10. If we reject the null hypothesis, we will assume the two treatments are equivalent with respect to survival, if we do not reject the null hypothesis, we will assume that SR is superior to SBRT with respect to overall survival.

To determine the sample size for the trial we assumed a significance level of 0.05, an HR of 1.60 (SBRT versus SR, for the null hypothesis) and set power to be 90%. We plan a single interim analysis when half of the expected events (deaths) have occurred; this will be for futility only. Assuming a 3-year survival rate of 0.80, a HR of 1.60 yields a 3-year survival rate for SBRT of 0.70 or less for the null hypothesis. Assuming an accrual rate of 10 patients per month, an expected accrual duration of 40 months (3 1/3 years), and a minimum follow-up of 42 months (3.5 years), the necessary sample size is 400 eligible patients (200 per arm). To ensure that there is an adequate number of eligible patients (including patient refusals after randomization and prior to treatment), we will have a target accrual that is approximately 5% greater than this or 420 patients. This trial is expected to accrue in approximately 40 months and the final analysis will occur after 166 deaths have been observed or about 82 months (6.8 years) after the first patient is enrolled.

In summary, a sample size of 200 eligible patients in each arm (target accrual is 420 including a 5% over accrual for patients who withdraw consent prior to treatment initiation) would mean that if the true hazard ratio is 1, then there is a 90% probability of declaring non-inferiority, and if the true hazard ratio is 1.6, there is a 5% probability of declaring non-inferiority.

## 10.3 Planned Analyses

### 10.3.1 Primary Endpoint Analysis

The primary analysis will exclude patients who cancel (withdraw consent) prior to receiving treatment; we will tabulate the number (percent) of patients who withdraw prior to treatment and take actions if this percent appears to be greater than 5%. Patients who are randomized but received the opposite treatment to which they were randomized will be included in the analysis according to the treatment they received; it is expected

that the rate of patient crossover will be low. However, a sensitivity analysis using the fully intention to treat approach will also be performed. The primary endpoint will be analyzed using a one-sided log-rank test comparing the overall survival of the two arms and a one-sided (upper boundary) 95% confidence interval (CI) for the HR. If the 95% CI for the HR lies entirely below 1.6, this will be evidence that SBRT is non-inferior to SR. If the interval includes 1.6, this is evidence that SBRT is inferior to SR.

### 10.3.2 Interim Analysis

While this trial is accruing, we will be closely monitoring Z4032 for the maturation of its results. The results of this trial are expected to be mature in 12/2011. If the analysis of Z4032 indicates that either SR alone or SR with brachytherapy is superior to the other, we will amend this trial to use the therapy found to be superior in Z4032 as the treatment in Arm 1 (the SR arm) of this trial. At this point, we would also amend the sample size based on the results of Z4032, if needed.

A single formal interim analyses for futility based on the primary endpoint will be conducted after 79 deaths have been observed. The rationale for performing a single interim analysis for futility is based on the following considerations: (1) there may be different time-related patterns of treatment-related mortality in the two arms, i.e., the hazards may not be proportional; (2) stopping early for non-inferiority before all patient have been randomized may be inappropriate given the potential importance of the adverse event profile and quality of life endpoints in deciding the preferred treatment; and (3) as a non-inferiority trial, early stopping for "success" (i.e. non-inferiority) is not ethically necessary and may undermine the general acceptance of the result. The interim analysis will take place after half the expected trial information (i.e. 79 deaths) has been observed.

Assuming a baseline rate of a three-year survival of 80% for the SR, a sample size of 400 provides 90% power to declare non-inferiority if the three-year survival rates are truly the same (i.e. HR = 1), using a one-sided logrank test with alpha = 0.05 for falsely declaring non-inferiority when the true three-year survival rate for the SBRT arm is 70%. The calculations are based on a two-sample survival non-inferiority calculation, performed using EAST version 4.0, with an 80% 3-year survival for the control arm, and a 10% non-inferiority margin. A single interim analysis for futility for the primary endpoint will be conducted after 79 deaths have been observed, using an O'Brien-Fleming stopping boundary. The Z-scale boundaries are 0.031, for the interim analysis, and 1.63 for the final analysis; these correspond to a p-value of 0.49 and HR of 1.59 for the interim analyses boundaries and a p-value of 0.052 and HR of 1.23 to reject non-inferiority (the alternative hypothesis).

### 10.3.3 Secondary Endpoint Analyses

Local-regional recurrence-free survival and disease-free survival will be compared using a one-sided log-rank test. As for the primary analysis, we will exclude patients who are randomized but then cancel and refuse the treatment to which they were assigned. We will also perform the fully intention to treat approach as a sensitivity analysis.

Analysis of the adverse event rates and PFT values will involve chi-square tests and t-tests and Wilcoxon procedures at each time point as well as a repeated measures analysis of variance (ANOVA) and general estimation equations (GEE) modeling using data from all timepoints. [126] Models will include covariates of patient characteristics as well as treatment arm to perform a conditional analysis of treatment comparison in the presence of potentially confounding variables. The extent of missing data will be explored for non-random influences. [127] Sensitivity analysis will be performed using various simple imputation techniques to ensure results are not unduly influenced by the presence of missing data. [128,129] We examine the impact of imputing using such methods as last-value-carried forward, nearest-neighbor imputation, zero-value imputation, minimum-value imputation, and maximum-value imputation on the result original analysis. The degree of variability in the results will allow for a calibration of the impact of the best and worst case scenarios in terms of patterns in the missing data on the stability of the analytical results.

A tertiary analysis is planned that will compare the adverse events and PFTs profiles in each arm for patients with low or high Charlson Comorbidity Index scores, including a test interaction between Charlson Comorbidity Index scores (low vs. high) and treatment arm. Again, we will use appropriate modeling techniques. Modeling techniques will also be used to determine other prognostic variables that might be used to determine other characteristics that are associated with outcome in the different treatment arms.

## 10.4 Monitoring

This study will be monitored by the ACOSOG Data Monitoring Committee. In addition, the study chair and study statistician will review this study twice per year in conjunction with production of the semiannual ACOSOG Group Meeting reports to identify any problems with accrual, toxicity, and endpoints. The study team will monitor the trial for evidence of severe adverse effects and feasibility problems.

# 11 Regulatory Considerations

## 11.1 Registering Physician

The investigator intending to register a patient to this study must be a member in good standing of the American College of Surgeons Oncology Group (ACOSOG) or endorsed by another cooperative group (ECOG, SWOG, CALGB, etc), if applicable. 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.

All enrolling 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 to the Pharmaceutical Management Branch.

## 11.2 Registering Institution

An ACOSOG member must enroll patients at clinical sites that have a valid assurance number from the United States Office for Human Research Protections (OHRP). Most institutions have a Multiple Project Assurance (MPA), Cooperative Project Assurance (CPA) number or Federalwide Assurance (FWA). 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.

## 11.3 Submission of IRB Approval

Documentation of IRB approval must be submitted to CTSU for entry into the Regulatory Support System (RSS) before patient registration will be allowed. Submission of subsequent annual renewals and amendment approvals is also required. Submission instructions and coversheets are available at https://www.ctsu.org/rss/.

## 11.4 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

There is no information currently available regarding differential effects of these regimens in subsets defined by race, gender, or ethnicity; and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for such subset analyses.

**Accrual by Gender and Racial/Ethnic Group**

| Ethnic Category | Gender | | | |
|---|---|---|---|---|
| | **Females** | **Males** | **Unknown** | **Total** |
| Hispanic or Latino | 4 | 4 | 0 | 8 |
| Not Hispanic or Latino | 199 | 213 | 0 | 412 |
| **Ethnic Category: Total of all subjects*** | 203 | 217 | 0 | 420 |
| **Racial Category** | | | | |
| American Indian or Alaskan Native | 2 | 2 | 0 | 4 |
| Asian | 6 | 6 | 0 | 12 |
| Black or African American | 17 | 11 | 0 | 28 |
| Native Hawaiian or other Pacific Islander | 2 | 2 | 0 | 4 |
| White | 176 | 196 | 0 | 372 |
| **Racial Category: Total of all subjects*** | 203 | 217 | 0 | 420 |

## 11.5 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/.

## 11.6 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 to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

# 12 Credentialing

**Prior to patient registration, participating physicians and sites must meet all the following credentialing requirements.**

## 12.1 Surgeon Credentialing

All surgeons' credentialing will be conducted by the study chair or designee.

### 12.1.1 Thoracic Surgery Credentialing

Participating surgeons must complete and submit the Z4099 Surgeon Credentialing Checklist available on the Z4099 page of www.acosog.org prior to registering a patient. Surgeons must meet one of the following criteria:

1. Membership in General Thoracic Surgery Club. Criteria for membership include:
    - Surgeons who have obtained specialty certification in thoracic surgery by the American Board of Thoracic Surgery or the Royal College of Surgeons, or other official certifying organization;
    - Surgeons who have been in practice for a minimum of two years beyond the completion of formal training in thoracic surgery, and devote at least 50% of their practice to general thoracic surgery;
    - Surgeons whose list of all operations performed in the year prior to application has been certified by the chief(s) of surgery at their institution(s).

2. Board-certified cardiothoracic surgeon with ≥ 50% of surgery practice devoted to general thoracic surgery.

NOTE: Surgeons who do not meet the above criteria must submit the following for review by the study chair:

- Case list of operative experience for the previous year
- Operative and pathology reports for five sublobar resection procedures done during the previous year

### 12.1.1 Brachytherapy Credentialing for Surgeons

Surgeons at sites who would like the option of using brachytherapy must complete and submit the brachytherapy portion of the Z4099 Surgeon Credentialing Checklist available on the Z4099 page of http://www.acosog.org prior to registering a patient. Each physician must meet one of the following criteria. Documentation specified for each criterion must accompany the checklist.

1. Enrolled a patient in ACOSOG Z4032 study. Emailed documentation of Z4032 participation will be provided to investigators and recorded in the database by ACOSOG. NOTE: If treatment planning or personnel have changed since participation in Z4032, then brachytherapy credentialing must be repeated.
2. Attended an ACOSOG Brachytherapy Workshop. Include emailed documentation from ACOSOG of attendance.
3. Viewed the training video on seed placement and successfully completed the quiz available on the Z4099 page of www.acosog.org. No documentation is necessary - the test results will be sent to the study chair for approval.
4. Observed a SR + brachytherapy case by an approved surgeon. Include written documentation of participation.

### 12.1.2 Surgeon Credentialing Submission Instructions

The Z4099 Surgeon Credentialing Checklist and all required supporting documents will be submitted via Fax or email to:

ACOSOG Site Coordinator

Phone: 507-284-9565

Fax: 507-293-1150

Email: rstacosogsite@mayo.edu

Credentialing materials will be routed to and reviewed by the Study Chair. The surgeon will be contacted if additional information is needed. Once credentialing requirements have been met, ACOSOG will notify the surgeon.

## 12.2 Radiation Oncology/Site Credentialing

### 12.2.1 Brachytherapy Credentialing for Radiation Oncology Departments

Credentialing for radiation oncology departments that intend to use brachytherapy on this study includes completion of a questionnaire and two test cases before patients may be treated. The questionnaire and information about the test cases are available at http://atc.wustl.edu.

The questionnaire requires information regarding personnel, the implant technique to be used, the treatment planning system, and quality assurance procedures.

The first test case is a calculation for a single seed of the same model that will be used for the site's patients. The questionnaire and first test case will be submitted via hardcopy to ITC. See submission instructions below.

For the second test case a post-implant CT scan of an actual implant will be downloaded from http://atc.wustl.edu and a treatment plan performed following the instructions on the website. The second test case will be submitted digitally to ITC.

Approval of the test cases will apply to the treatment planning system and seed model that were used. A change in either the planning system or the seed model will require resubmission of the questionnaire and the first test case. A change in planning system will also require resubmission digitally of the second test case.

The completed questionnaire and test cases will be reviewed by the radiation oncology co-chair(s) or designee. The co-chair will contact the site if additional information is needed. Once credentialing requirements have been met, the co-chair will notify the ACOSOG Site Coordinator, who will notify the site.

NOTE: If the institution has participated in Z4032 and successfully submitted digitally one or more cases, only the questionnaire and first test case need to be submitted. If the treatment planning system, brachytherapy source or personnel has changed since participation in Z4032, then the second test case must be submitted as well.

The questionnaire and first test case will be submitted as hard copies. The second test case must be submitted digitally in DICOM RT format. Submission by either CD or SFTP is supported. See Site Credentialing Submission Instructions (Section 12.2.3).

### 12.2.2 SBRT Credentialing for Radiation Oncology Departments

Credentialing for stereotactic body radiation therapy and heterogeneity corrections by the Radiological Physics Center (RPC) is necessary prior to enrolling patients on this study.

All participating institutions must use the AAA, superposition/convolution or Monte Carlo based dose calculation algorithms. Institutions wishing to submit IMRT plans must also be credentialed for intensity modulated radiotherapy (IMRT) prior to enrolling patients on this study. Instructions for completing these requirements or determining if they already have been met are available on the RPC web site at http://rpc.mdanderson.org/rpc. Select "Credentialing" and "Credentialing Status Inquiry".

SBRT credentialing includes the steps outlined below. Centers previously credentialed for some of the technologies/procedures involved may not have to be re-credentialed. However, institutions not using superposition/convolution algorithms that were previously credentialed to use Clarkson or pencil beam algorithms for SBRT on RTOG 0236 will be required to be re-credentialed for heterogeneity corrections. In addition, institutions that have changed the technology/procedures previously credentialed (i.e., fundamentally change methods like changing from tracking to abdominal compression for motion control) must be re-credentialed with their new systems. Institutions that have changed from standard IMRT to Tomotherapy, CyberKnife® or volume arc IMRT delivery will require re-credentialing.

**SBRT Credentialing Process**

1. **Obtain SFTP Account.** A Secure FTP (SFTP) account with username and password can be obtained by contacting the ITC at (314) 747-5415 or itc@wustl.edu. Guidelines for digital submission are available at http://atc.wustl.edu.
2. **Complete Facility Questionnaire.** Each participating institution must complete a Facility Questionnaire available on http://atc.wustl.edu. Information in a previous Facility Questionnaire can be extended to meet this requirement by simply adding data that is specific to this SBRT protocol. All questions in the Facility Questionnaire pertaining to IMRT (if this treatment modality is to be used), heterogeneity corrections, respiratory movement control, and IGRT must be answered.
3. **Complete Knowledge Assessment.** Each participating institution must complete a Knowledge Assessment questionnaire available at http://atc.wustl.edu. This questionnaire verifies the investigator's knowledge of the protocol. NOTE: Questions pertaining to brachytherapy also are included in the assessment.
4. **Perform IGRT Verification Study.** Each institution must perform a verification study demonstrating their ability to reproducibly register daily IGRT information with a planning CT dataset (i.e., the gross tumor volume falls within the CT simulation defined PTV). The patient used for this verification procedure must have a target in the lung that is similar to the lesions that will be treated for patients entered on this study. The information submitted must include three (3) IGRT datasets (from three (3) different fractions) for a single anonymized patient and must employ the method that will be used for respiratory control for patients entered from a particular

institution. This information with a spreadsheet (the spreadsheet is available on the ATC web site, http://atc.wustl.edu) will be reviewed by the Medical Physics Co-Chair.

5. **Irradiate Phantom.** Each participating institution must irradiate a standardized phantom provided by RPC. Instructions for requesting and irradiating the phantom are available at the RPC web site, http://rpc.mdanderson.org/rpc/ by selecting "Credentialing" and "ACOSOG." The phantom simulates a lung tumor within lung tissue equivalent material.

   This trial allows IMRT techniques (including CyberKnife® and Tomotherapy), and the phantom irradiation requirements vary according to the combination of delivery technique and respiratory control methodology. In general, institutions using conformal techniques and abdominal compression for respiratory motion control together with the recommended margins will irradiate the stationary version of the phantom. The exception is for institutions intending to use either tracking or gating techniques when lesions do not remain within the stated margins. These institutions will be required to irradiate the moving phantom for credentialing. Additionally, institutions using CyberKnife® or Tomotherapy delivery will be required to irradiate the moving phantom for all methods of respiratory control. The RPC will provide assistance to help the institution determine the appropriate phantom irradiation technique.

The credentialing materials will be reviewed by the study team. The site will be contacted if additional information is needed. Once credentialing requirements have been met, RTOG will notify the ACOSOG Site Coordinator, who will notify the site.

### 12.2.3 Site Credentialing Submission Instructions

**Brachytherapy**: The questionnaire and first test case will be submitted as hard copies. The second test case must be submitted digitally in DICOM RT format.

**SBRT**: The treatment planning CT, treatment plan (CT files, dose files, plan files, and structure files) and other required materials must be submitted digitally as DICOM RT. The irradiated phantom will be submitted to ITC as well. Forms and questionnaires may be submitted electronically (if available) or as hard copies.

All submissions via CD or hard copy should be submitted to:

Image-guided Therapy QA Center

4511 Forest Park Ave, Suite 200

St. Louis, MO 63108

Phone: (314) 747-5415

Fax: (314) 747-5423

Email: itc@wustl.edu

An SFTP account (username and password) can be obtained by contacting the ITC at (314) 747-5415 or itc@wustl.edu. Guidelines for digital submission are available at http://atc.wustl.edu.

Sites must notify ITC via e-mail when digital data are submitted. The e-mail must include the study number and a description of the datasets being submitted (e.g., Z4099 radiation oncology brachytherapy credentialing, Z4099 SBRT credentialing, phantom, etc.).

# 13 Biospecimen Collection

All patients should be offered the option to have biospecimens collected for the specific correlative studies embedded in this protocol and for banking and use in future, retrospective studies. **Note that patients may consent to the use of their biospecimens for the specific correlative studies in this protocol, independent of biospecimen banking for future, unspecified use. Also note that a patient may still participate in the clinical trial even if they refuse to consent to any biospecimen collection, as biospecimen collection is not integral to the clinical trial design.**

All specimens will be stored and governed by the ACOSOG Central Specimen Bank (CSB) at Washington University in St. Louis and the ACOSOG Central Specimen Bank and Pathology Committee. Every effort will be made to ensure that adequate banked samples remain at the CSB for future studies. These specimens are a valuable resource. Proper utilization of this resource will be assured by the stringent oversight and Standard Operating Procedures of the CSB.

## 13.1 Required Specimens

All supplies for collecting and shipping specimens will be provided and distributed by the ACOSOG Central Specimen Bank (see Specimen Shipping, Section 13.3).

### 13.1.1 Blood Specimens for Biospecimen Banking and Correlative Science Studies

If consent is obtained, patients should have peripheral whole blood specimens collected by routine venipuncture at the following time points:

- **Before surgery (Arm 1) or SBRT (Arm 2). Note: This specimen may be collected prior to the date of surgery or at the time of surgery (i.e., after induction of anesthesia per patient preference).**

  Two, 10 ml lavender top (K-EDTA) tubes and one 10 ml red top (no additive) tube. One tube of whole blood will be sent to the CSB for genomic DNA isolation. The remaining two tubes should be processed on site for plasma (K-EDTA) and serum (no additive) isolation, respectively. Aliquoted frozen plasma and serum will be shipped to the CSB.

- **First post-operative visit at 4 weeks (Arm 1)**

  One 10 ml lavender top (K-EDTA) tubes and one 10 ml red top (no additive) tube. The two tubes should be processed on site for plasma (K-EDTA) and serum (no additive) isolation, respectively. Aliquoted frozen plasma and serum will be shipped to the CSB.

- **Before (same day) final SBRT treatment (Arm 2)**

  One 10 ml lavender top (K-EDTA) tubes and one 10 ml red top (no additive) tube. The two tubes should be processed on site for plasma (K-EDTA) and serum (no additive) isolation, respectively. Aliquoted frozen plasma and serum will be shipped to the CSB.

- **Every 6 months for 2 years, then yearly to 5 years (Arms 1 and 2)** Note: No additional samples are required after disease progression/relapse.

  One 10 ml lavender top (K-EDTA) tubes and one 10 ml red top (no additive) tube. The two tubes should be processed on site for plasma (K-EDTA) and serum (no additive) isolation, respectively. Aliquoted frozen plasma and serum will be shipped to the CSB.

### 13.1.2 Tissue Specimens for Biospecimen Banking

If consent is obtained, snap frozen tissue specimens from the surgical resection (Arm 1) should be collected using the procedures described below.

### 13.1.3 Summary of Required Biospecimen Types

| Time Point | Material | Quantity | Kit | Shipping |
|---|---|---|---|---|
| Pre-intervention<br>(Arms 1 and 2) | Whole blood<br>Frozen plasma<br>Frozen serum | 1, 10 ml KEDTA tube<br>1, 10 ml KEDTA tube<br>1, 10 ml no additive tube | A | Spin, aliquot, and freeze serum and plasma<br>Ship immediately to ACOSOG CSB |
| Post-op visit at 4 weeks<br>(Arm 1) | Frozen plasma<br>Frozen serum | 1, 10 ml KEDTA tube<br>1, 10 ml no additive tube | C | Spin, aliquot, and freeze serum and plasma<br>Hold or Ship immediately to ACOSOG CSB |
| Before final SBRT (same day)<br>(Arm 2) | Frozen plasma<br>Frozen serum | 1, 10 ml KEDTA tube<br>1, 10 ml no additive tube | C | Spin, aliquot, and freeze serum and plasma<br>Hold or Ship immediately to ACOSOG CSB |
| Every 6 mo. x 2 years<br>Yearly until 5 years<br>(Arms 1 and 2) | Frozen plasma<br>Frozen serum | 1, 10 ml KEDTA tube<br>1, 10 ml no additive tube | C | Spin, aliquot, and freeze serum and plasma<br>Hold or Ship immediately to ACOSOG CSB |

## 13.2 Specimen Collection and Processing

Additional information regarding procedures for biospecimen collection and processing can be found in the ACOSOG Specimen Bank SOP, which is located on http://www.acosog.org. Procedures relevant to this protocol are summarized here.

### 13.2.1 Whole Blood

One 10 ml KEDTA (lavender top) tube of whole blood should be collected by standard venipuncture. The tube should be inverted thoroughly for 30 sec. to prevent coagulation. The tube should be labeled with that patient's ACOSOG ID number and the date and time of collection. Whole blood should be maintained at room temperature and shipped to the ACOSOG CSB within 24 hours of the time of collection. Once received by the CSB, whole blood will be spun and the peripheral blood nucleated cell layer (buffy coat) isolated, aliquoted, and snap frozen. Frozen peripheral blood nucleated cells will be used for subsequent genomic DNA isolation.

### 13.2.2 Plasma

One 10 ml KEDTA (lavender top) tube of whole blood should be collected by standard venipuncture. The tube should be inverted thoroughly for 30 sec. to prevent coagulation. The tube should be labeled with the patient's ACOSOG ID number and the date and time of collection. Ideally, processing should be done within 2 hours of collection. Plasma should be isolated by centrifugation at 3,000 x G for 30 minutes in a refrigerated clinical centrifuge. Resulting plasma should be withdrawn in 1 ml increments, avoiding contamination with the 'buffy coat' or red cell layer, and transferred to cryovials. At least 3, but as many as 5, 1 ml aliquots should be created. Each cryovial should be legibly labeled with the ACOSOG patient study number and time point of blood draw. Cryovials containing 1 ml plasma aliquots should then be immediately frozen in liquid nitrogen vapor or a dry ice bath. If neither source is available, plasma may be frozen by placing in a -70$^{o}$C or colder electrical freezer. **Do not immerse vials in liquid nitrogen. Do not freeze plasma by placing in a -20$^{O}$C freezer**. The date and time at which the plasma is finally frozen should be recorded on the CRF. **It is important to accurately document the time interval between blood collection and final freezing of the plasma.** Frozen plasma should be stored on dry ice, in a -70$^{o}$C electrical freezer, or in liquid nitrogen vapor phase until ready for shipment. If aliquots from multiple patients or multiple time points are to be stored locally and shipped in batch, it is important that each aliquot vial be clearly labeled with the ACOSOG ID and the blood collection time point.

### 13.2.3 Serum

One 10 ml plain glass (no additive) tube of whole blood should be collected by standard venipuncture. The tube should be inverted thoroughly for 30 sec. and blood should be allowed to clot. The tube should be labeled with that patient's ACOSOG ID number and the date and time of collection. Ideally, processing should be done within 2 hours of collection. Serum should be isolated by centrifugation at 3,000 x G for 30 minutes in a refrigerated clinical centrifuge. Resulting serum should be withdrawn in 1 ml increments, avoiding contamination with the 'buffy coat' or red cell layer, and transferred to cryovials. At least 3, but as many as 5, 1 ml aliquots should be created. Each cryovial should be legibly labeled with the ACOSOG patient study number and time point of blood draw. Cryovials containing 1 ml serum aliquots should then be immediately frozen in liquid nitrogen vapor or a dry ice bath. If neither source is available, serum may be frozen by placing in a -70$^{o}$C or colder electrical freezer. **Do not immerse vials in liquid nitrogen. Do not freeze serum by placing in a -20$^{O}$C freezer**. The date and time at which the serum is finally frozen should be recorded on the CRF. **It is important to accurately document the time interval between blood collection and final freezing of the serum.** Frozen serum should be stored on dry ice, in a -70$^{o}$C electrical freezer, or in liquid nitrogen vapor phase until ready for shipment. If aliquots from multiple patients or multiple time points are to be stored locally and shipped in batch, it is important that each aliquot vial be clearly labeled with the ACOSOG ID and the blood collection time point.

### 13.2.3 Frozen Tissue

After surgical resection, the specimen(s) should be brought to the pathology department as soon as possible (generally speaking, this means within 15 minutes after the time of tissue resection). **If possible, in order to accurately record the *ex vivo* ischemia time, the time at which the specimens are excised from the patient should be recorded.** The specimen(s) should be kept fresh and not put into any type of fixative, although it may be transported to pathology in a solution of normal saline or any other physiologic buffer. The specimens should be reviewed by the attending pathologist or other authorized individual (pathology resident, fellow, or qualified pathologist assistant). Material needed for diagnosis should be removed and processed according to the institution's standard procedures. Any remaining tissue may be sent to the ACOSOG Central Specimen Bank.

Where possible, representative and grossly apparent tumor tissue and organ-matched non-malignant tissue **at least 2 cm distal from the tumor margin** should be collected. Tissue that is grossly necrotic, hemorrhagic, or cauterized should be avoided. Tissue should be rapidly divided into segments no larger than 1 $cm^3$ (1 gram). As many (but at least one) of these sized segments should be collected, if possible. If appropriate, procurement of tissue can be facilitated by using a sterile skin punch biopsy tool included in the specimen kit. Areas identified by gross inspection can be 'punched' with the disposable instrument. The resulting tissue "plugs" can then be ejected from the punch. An independent punch tool should be used for each specimen type sampled (i.e. tumor versus non-malignant tissue) to avoid cross-contamination.

Place the tissue segments in the tissue cassettes provided (usually 2-3 segments of tissue per cassette). Use multiple cassettes if necessary - do not 'stuff' large amounts of tissue into a single cassette. Label the cassette with 'T' for tumor or 'N' for non-malignant tissue using the marker provided. Wrap each cassette in a piece of foil (provided in the kit). Place the cassette at one end of the foil and roll the foil around the cassette. Carefully fold over the ends of the foil and crease them tightly to create a sealed, compact packet. Immediately immerse the foil-wrapped cassette in liquid nitrogen for 5 minutes. If liquid nitrogen is not available, the specimen may be immersed in an isopentane cryobath available in most surgical pathology frozen section rooms. If using a cryobath, be certain that the temperature of the bath is at or below -40°C. As a last option, specimens may be frozen by complete immersion in an ethanol / dry-ice bath. Specimens should be left in the cryobath or dry ice bath for at least 15 minutes to ensure complete freezing. Specimens should not be frozen by placing fresh tissue in a -80°C freezer or inside a cryostat. **The time at which the tissue is frozen should be recorded so that, together with the recorded time of operative resection, the *ex vivo* warm ischemia time can be calculated.**

Once frozen, foil- wrapped tissue cassettes should be placed in one or more of the zip-lock bags provided. Be certain that the specimen bag is accurately and legibly labeled with the ACOSOG patient ID number. Once frozen, tissue may be stored in a -80°C mechanical freezer until shipping. Once frozen, take extreme care not to let the tissue specimen thaw.

## 13.3 Specimen Shipping

All biospecimen procurement and shipping supplies are available (at no cost) from the CSB. The submitting institution should contact the CSB at least 1 week prior to patient enrollment to request appropriate procurement and shipping materials. The CSB will provide up to three shipping kits to a site. Additional kits may be requested upon receipt of a completed, returned kit. **Note that all components of the kit (including the outside box itself) are used for return shipment and are recyclable. Do not dispose of any kit component or shipping material.** Specific instructions for packing and shipping biospecimens are included in each biospecimen collection kit.

This protocol uses three different kits and shipments to collect biospecimens:

A. Shipping kit to collect whole blood at ambient temperature and aliquots of frozen plasma and serum.

B. Shipping kit to collect frozen tissue and aliquots of frozen plasma and serum (Arm 1 only)

C. Shipping kit to collect aliquots of frozen plasma and serum

The general format of each kit is the same, but each contains slightly different contents to collect the material required for the requisite study arm and timepoint.

Note that each shipment must be accompanied by a corresponding CRF for the ACOSOG CSB. A copy of each submission form should be retained in the site's records for entry into the ACOSOG database.

If facilities are available, aliquots of frozen serum and plasma from multiple patients or multiple time points may be stored locally and shipped in batches on a regular basis. In this case, it is important that each aliquot vial be clearly labeled with the ACOSOG ID and the blood collection time point and that each set of frozen specimen aliquots be accompanied by a separate CRF form to indicate the patient and time point with which they are associated. Also, standard kits are not designed to accommodate a larger number of frozen aliquot vials. **If a site prefers to batch ship specimens, please contact the CSB for appropriate instructions and shipping containers.**

Specimens may be sent to the CSB on Monday through Friday for next day delivery. The CSB cannot receive specimens on Sundays or holidays. **Do not send specimens on Saturday or the day before a holiday.**

Arrange for Federal Express pick-up through your usual institutional procedure. Ship CSB specimens to:

Mark A. Watson, M.D., Ph.D.

ACOSOG Central Specimen Bank

Room 2316 Kingshighway Bldg.

Barnes-Jewish Hospital North

216 S. Kingshighway

St. Louis, MO 63110

Phone: (314) 454-7615

Fax: (314) 454-5525

E-mail: watsonm@pathbox.wustl.edu

On the day that specimens are sent to the Specimen Bank, please contact the bank by phone, fax, or e-mail to notify what is being sent and when the shipment is expected to arrive.

# 14 Correlative Science Studies

The purpose of these correlative studies is to evaluate the impact of patient-reported outcomes and biologic variables on study endpoints.

## 14.1 Quality-Adjusted Survival and the Impact of Clinically Significant Deficits in Patient-Reported Outcomes for Patients with Non-Small Cell Lung Cancer and N2/N3 Negative Lymph Nodes

**Study Design**

Completion of the quality of life questionnaires is required for all patients. Completed questionnaires will be collected by research staff and entered into the ACOSOG database.

Patients will complete questionnaires at the following time points:

- After registration and before surgery or SBRT
- At 4 weeks post-op (Arm 1) or post-SBRT (Arm 2)
- From date of surgery/end of SBRT: At 3 months, 6 months, 12 months and 24 months

As a phase III randomized clinical trial with a non-inferiority design for time to recurrence and time to death, the comparative effectiveness of these two treatment regimens will likely be a function of the impact each has on patient well-being and symptomatology. We propose to conduct a correlative study based on patient reported outcome (PRO's) that will accomplish the following goals:

1. Explore the use of PRO-based evaluation of comparative effectiveness among alternative surgical or complex multi-disciplinary treatments to augment or supplement the survival endpoints. Augmentation will take the form of improved primary analyses using techniques such as quality-adjusted survival estimates to incorporate the patient's perspective into treatment evaluation of survival. Supplementation will take the form of secondary analyses comparing alternative treatments for survival using PRO domains as covariates.
2. Explore the impact that changes in PRO-related domains have on surgical treatment and adjuvant treatment outcomes, including survival.
3. Build a repository of normative data for surgical oncology patients with lung cancer so that future trials can be informed as to which covariates are important and at which time points. Further this normative data will allow the identification of opportunities for considering interventions to that would specifically address PRO-related deficits.

We have chosen PROs as they have been demonstrated to be the optimal way to capture patient well-being, be it overall quality of life, one of the five sub-domains (physical, emotional , intellectual, spiritual, social), or symptom burden [1]. PRO-based symptom assessment has proven to be superior in terms of sensitivity, specificity and responsiveness [2]. Speaking to the importance of PRO's there are several studies that have recently demonstrated that PRO's are prognostic for survival across a broad spectrum of cancer patient populations in retrospective meta-analyses [3, 4, 5, 6]. The advances in PRO research have seen relatively sparse application in surgical cancer patients. There are several reasons for this including barriers to access to patient populations and a lack of expertise among clinical investigators. This effort will be the first to prospectively examine the relationship between PRO's and surgical outcomes, including survival.

The QOL team of ACOSOG is well positioned to conduct these studies as they have pioneered the use of a responder-type investigation wherein we a priori define a clinically significant effect size a priori and compare treatments in terms of the response rate for clinically significant deficits in PRO domains [7, 8, 9]. This deficit is defined at baseline as a score of 0-5 on a 0-10 numerical analogue scale where the relevant PRO domain is rated as 0 by the patient to represent the PRO domain is as bad as it can be and 10 represents the situation where the patient perceives that the PRO domain is as good as it can be. Longitudinally, a clinically significant shift is defined as a change of 2 points on the 0-10 point scale which is equivalent to a full standard deviation shift over time. For some applications a minimally significant change over time has been defined as a single point change [10].

Patients will complete questionnaires at the timepoints described above. These assessments can be made remotely via telephone, interactive voice-recognition software (IVRS), or internet access as well as in person. An assessment of health status (via the EQ-5D) [17] will allow for the construction of quality-adjusted life-year survival estimates (QALYs) [11]. Other lung cancer-specific symptom-related burden will be assessed via the Lung Cancer Symptom Scale [11]. All of the items involved have been validated for use in lung cancer patient populations, and the single-item assessments have demonstrated prognostic power for survival in other patient populations [1, 12, 16]. Through these simple single-item PRO assessments, patients are defined as having clinically significant deficits in each domain (overall QOL, fatigue, anxiety as defined as a score of 5 or less on a 0-10 scale). Dyspnea will be measured using the UCSD Shortness of Breath Questionnaire [21], which has also been validated for use with lung cancer patients.

**Specific Aims**

The specific aims of this correlative study are:

1. To compare the quality-adjusted survival between the treatments SBRT and SR in terms of time to death (primary) and time until local recurrence (secondary).
2. To compare the quality-adjusted survival between the treatments SBRT and SR in terms of time to recurrence (primary) and time until death (secondary).
3. To examine whether pre-operative and post-operative clinically significant deficits in previously-identified prognostic PRO domains (overall QOL, fatigue, anxiety, symptoms) are associated with shorter patient survival in this patient population and to compare the relative effectiveness of each treatment (SBRT and SR).
4. To contribute to an ACOSOG bank of normative data in order to improve short/long term outcomes of cancer patients by identifying patients experiencing clinically significant deficits in patient-reported outcomes and the relationship to genetic variables.

The following PRO assessments are included in this trial (rationale for inclusion above):

**EQ5D [**17] – The EQ5D is a five-item standardized instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. It is one of the most commonly-used and well validated measures used in QALY studies. Detailed information of its extensive history and normative data are available at http://www.euroqol.org.

**Lung Cancer Symptom Scale (LCSS) [**11] - The LCSS is designed as a site-specific measure of quality of life (QL), particularly for use in clinical trials. It evaluates six major symptoms associated with lung malignancies and their effect on overall symptomatic distress, functional activities, and global QL. The philosophy behind the development of the LCSS is to provide a practical QL measure that reduces patient and staff burden in serial measurement of QL during the course of the trial. It captures in detail those dimensions most likely to be influenced by therapeutic interventions and evaluates other dimensions globally. Detailed information on this extensively used assessment is available at http://www.lcss-ql.com.

**Linear Analogue Self-Assessment (LASA)** items [15, 16] – three items using a 0-10 numerical response scale will ask patients to rate their overall QOL, fatigue and anxiety. Detailed information on the LASA measures is available at http://www.qolpro.org.

**UCSD Shortness of Breath Questionnaire** [21] - Dyspnea will be measured using the UCSD Shortness of Breath Questionnaire. 24 items with a 0-5 numerical response scale will ask patients how short of breath they become with common daily activities, and how much the shortness of breath impacts their life overall. This validated instrument has been used in many trials of patients with severe lung disease.

Spanish translations are available for the EQ5D, LCSS and LASA assessments.

**Statistical Design**

The primary endpoint for this PRO correlative study will be the QALY estimate formed by the combination of the time to death data and the PRO health status assessments of the EQ-5D. Sloan described the detailed process of constructing QALYS and the related analysis that will be used in this protocol.[1] The comparison of the average QALY for time to death will be carried out via the appropriate simulation studies per Cole[13]

and sensitivity analysis in the form of Q-TWiST plots set out by Sloan[14]. The secondary endpoint of time until recurrence will be analyzed in the same fashion as the primary endpoint.

Goals 2-4 will attempt to integrate the PRO and survival endpoints into a combined analysis. The primary endpoint for this aspect of the study will be the QALY estimate formed by the combination of the time to recurrence data and the PRO health status assessments of the EQ-5D. Sloan described the detailed process of constructing QALYS and the related analysis that will be used in this protocol [1]. The comparison of the average QALY for time to recurrence will be carried out via the appropriate simulation studies per Cole [13] and sensitivity analysis in the form of Q-TWiST plots set out by Sloan [14]. Further, a new method will be applied to calibrate QALY scores to facilitate their interpretation developed by the ACOSOG statistical group which was presented at ASCO in June 2010 [17]. The secondary endpoint of time until death will be analyzed in the same fashion as the primary endpoint.

The secondary endpoints related to the LCSS and UCSD items and PRO domains of overall QOL, fatigue and anxiety will be compared across treatment arms by creating a pro-rated area under the curve statistic for each patient for each domain measured and using a two-sample t-test.

The impact of baseline (pre-operative) deficits in PRO domains for the LCSS and UCSD items and three single-item PRO domains (overall QOL, fatigue, anxiety) on the two time-related endpoints (time to recurrence and time to death) by incorporating these variables as covariates in the Cox model analyses specified in the main body of the concept.

Missing data are always a consideration on PRO-related studies. Our statistical group has extensive experience and has developed numerous standardized algorithms for dealing with missing data [18]. These algorithms described by Sloan et al [19], involve sensitivity analysis to test for nonrandom influences that might be producing the missing data and the use of alternative imputation methods to ensure that the results of the treatment comparison are robust relative to the presence of the missing data.

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## 14.2 Biomarkers of Tumor Recurrence and Treatment Toxicity

### 14.2.1 Study Design

All consenting patients will undergo collection of whole blood, serum, and plasma. For patients randomized to receive surgery, venous blood will be drawn pre- or intraoperatively and at the first post-op visit. For patients randomized to receive SBRT, venous blood will be drawn pretreatment, and immediately before the final SBRT treatment. Follow-up blood draws will be the same for all patients: q 6 months for 2 years, then yearly.

For Hypothesis A, blood markers will be correlated with time to tumor recurrence.

For Hypothesis B, blood based markers prior to, during and after treatment will be correlated with pulmonary complications (defined as grade $\geq$ 3 events).

### 14.2.1 Hypothesis A: Blood based biomarkers, including osteopontin, will be able to predict which patients will be at high risk for recurrence by treatment with either SBRT or Surgery.

**Introduction and Rationale**

Resection alone is the standard of care for stage I NSCLC, but 27-55% of patients will develop loco-regional recurrence,[25-27] indicating a subgroup within this population which would benefit from additional therapies. In other solid tumors, biomarkers exist which aid in diagnosis, reliably define response to therapy, and serve as a marker for recurrence. The most clinically relevant of these include prostate specific antigen (PSA) in prostate cancer, carcinoembryonic antigen (CEA) in colon cancer[28] and cancer antigen 125 (CA-125) in ovarian cancer. No such marker exists for NSCLC. Hypermethylation of promoters, mutations in K-ras and p53, and protein biomarkers such as CEA, cytokeratin 19 fragment (CYFRA 21-1), plasma kallikrein B1, and neuron-specific enolase[29] have all been investigated, but currently lack clinical utility.

Osteopontin (OPN) is a multifunctional glyco-phosphoprotein originally described as a secreted protein from malignant epithelial cells.[30] It is identified in a remarkable range of normal and pathologic contexts,[31] and is an important adhesive bone matrix protein which plays a key role in the mediation of immune cell recruitment, wound healing, and tissue remodeling.[32, 33] OPN's diverse biologic functions relate to cell adhesion, migration, and invasion; and are mediated by integrin receptor binding and activation of its two highly preserved central binding domains.[34]

OPN's importance in carcinogenesis and tumor dissemination is highlighted by gene transfer experiments where transfection of OPN increases the malignant phenotype,[35] and transfection with antisense oligonucleotides against OPN decreases malignant potential.[36, 37] OPN also plays an important but poorly understood role in NSCLC pathogenesis, and is strongly overexpressed by immunohistochemistry in NSCLC tumors compared to normal lung tissue.[38] Elevated plasma OPN levels in early stage NSCLC patients are associated with increased hypoxic tumor conditions and an increased risk of recurrence.[39] In advanced disease, elevated plasma OPN correlates with decreased response to therapy and poor prognosis.[40]

The utility of OPN as a biomarker has been investigated in other solid tumors. In malignant pleural mesothelioma, plasma OPN is significantly higher than in asbestos exposed patients without cancer. Cut point analysis has demonstrated that OPN values above and below 250 ng/ml are strongly associated with survival in mesothelioma, characterizing this protein as a useful clinical biomarker with prognostic significance.[41] The utility of plasma OPN levels to differentiate patients with early stage NSCLC from smokers and high-risk populations, or as a marker of response to therapy, has not been previously investigated. Although elevated plasma OPN is not unique to NSCLC, OPN appears to play a critical role in NSCLC carcinogenesis, and plasma levels have the potential to serve as an important biomarker in early stage disease. We hypothesize that plasma OPN levels are elevated in early stage NSCLC compared to high-risk patients without cancer, and that resection results in a measurable reduction of the biomarker.

Our preliminary data regarding OPN and lung cancer have been published recently in the Journal of Clinical Oncology[19]. Pre-operative (pre-op) plasma OPN levels (ng/mL) were measured by ELISA (IBL, Japan) in a discovery set of 60 early stage NSCLC patients and compared to 56 cancer-free smokers. Pre-op OPN was validated in an independent cohort of 96 resectable NSCLC patients. The pre-op OPN level in the latter cohort was compared to matched postoperative (post-op) OPN levels. Perioperative OPN levels were correlated with patient demographics, tumor characteristics and peri-operative events. The discovery set pre-

op OPN (271±31) in NSCLC patients was significantly higher than in smokers (40±2, p=0.001). Pre-op OPN was similar in the NSCLC validation cohort (324±20, p=0.134). Post-op OPN (256±21) measured at mean of 9.8 weeks (range 2-46) was significantly lower than pre-op (p=0.005). Time from surgery significantly impacted post-op OPN: OPN≤6 weeks post-op (303±26) was higher than OPN>6 weeks post-op (177±29) (p=0.003).

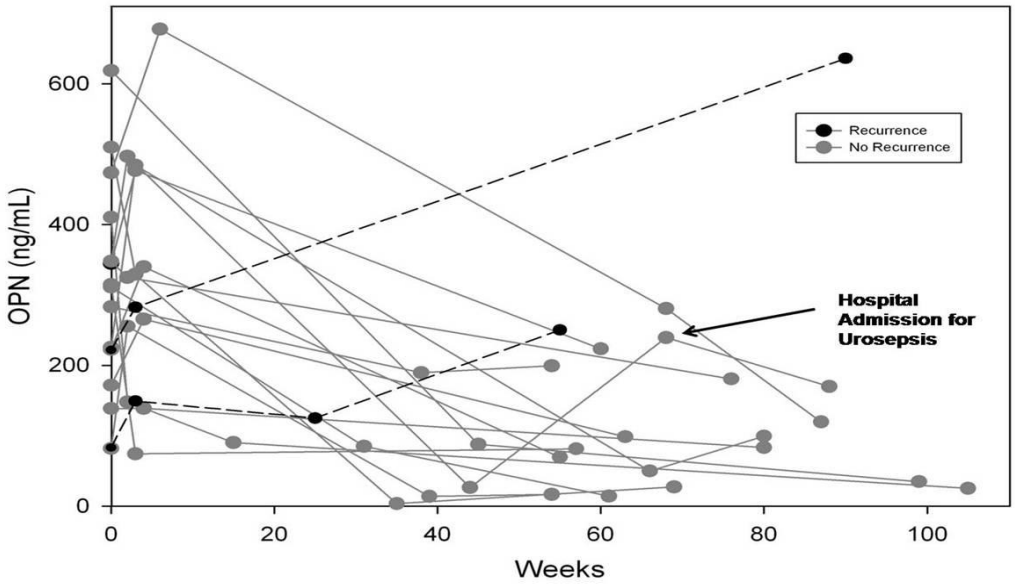


Figure 1. Longitudinal trends in post-op plasma OPN; each point represents post-op OPN measurements plotted against time from surgery for all patients with follow up greater than 52 weeks. In patients without recurrence, peri-operative fluctuations subside by 6 weeks and levels remain below 200ng/ml. Patients with recurrence had an accompanying rise in plasma OPN from their post-op nadir.

In two patients with documented recurrence (Figure 1), plasma OPN was elevated to greater than the postsurgery nadir at the time of recurrence. This provides preliminary evidence of a relationship between plasma OPN levels and NSCLC recurrence that warrants additional investigation. Although the utility of biomarker elevation alone as a trigger to initiate therapy is of questionable value, its utility in helping to determining recurrence with other clinical indicators has significant merit. Hence, plasma OPN levels are elevated in early stage NSCLC patients and are significantly reduced following resection. Peri-operative reductions in plasma OPN may serve as a marker for response to therapy.

**Research Plan**

Plasma OPN level determination will be performed either via multiplex Luminex assay or by individual ELISA. The advantage of the luminex assay would be that multiple biomarkers could be evaluated in a longitudinal fashion and also serve as the same platform for translational Hypothesis B. The NYU Thoracic Laboratory is expert in both OPN ELISA as well as Luminex assays.

There will be roughly 200 patients per arm randomized for this trial, and it is expected that baseline samples will be collected from nearly 100% of the registered patients. We anticipate that follow-up samples will be available from 80 to 100% of the patients. Hence, it is anticipated that a training set of 120 patients in each arm will be used to predict those biomarkers, including OPN, which are associated with recurrence by radiologic and histologic criteria, and a test set of 80 patients will be used for further validation of the profile(s) discovered in the training set.

### 14.2.2 Hypothesis B: Blood based biomarkers, including TGF-β1, will be able to predict which patients will be at high risk for pulmonary complications by treatment with either SBRT or Surgery.

**Introduction and Rationale**

Severe pulmonary complications occur in about 10-20% patients after lobectomy, [42-48] 5-10% after SR, while grade $\geq$ 3 radiation induced lung toxicity occurs in 10% patients treated with SBRT. [49-51] Currently, there are no means to predict which patient will develop such toxicity which patient will not. In general, the risk of pulmonary toxicity increases in patients with inadequate pulmonary function reserve, larger tumor size/larger treatment volumes, and use of chemotherapy. Many lung dosimetric factors, such as volumes receiving greater than certain dose (such as V30, V20, V13, and V5), the doses to a specific portions of the lung volume (such as D30), and mean lung dose (MLD) [52-59] were significantly associated with the risk of lung toxicity after radiation for populations of patients. However, a statistically significant association or description of complication rates for populations of patients is not the same as a good predictor for a given patient. For example, V13, V20, and MLD are significantly associated with radiation pneumonitis, but they all have a suboptimal predictive ability for individuals. [59] This is most likely from the complexity of underlying pathogenesis, which has not yet clearly defined, but apparently associated with involvements of multiple cytokines and yet to be defined signaling pathways. [60] Several reports have suggested a possible role of profibrogenic and proinflammatory cytokines in the modulation of radiation pulmonary injury including (by not limited to) Interleukin-1 (IL-1), IL-6, IL-8, IL-10, TNF-α, platelet-derived growth factor and Transforming growth factor beta 1 (TGFβ1).[61-69] Amongst these factors, TGFβı, a prototype of multifunctional regulators of cell growth and differentiation produced by fibroblasts, macrophage and sometime tumor cells activated by ionizing radiation-induced free radicals, is the most extensively studied cytokine for radiation induced lung toxicity (RILT). TGFβı stimulates connective tissue formation and decreases collagen degradation resulting in fibrosis and plays an important role in the inhibition of epithelial cell proliferation and the development of lung fibrosis associated with radiation pneumonitis and fibrosis. Researchers from Duke University reported that the plasma TGFβı level at the end of radiation correlated with symptomatic lung toxicity in patients treated with definitive radiation therapy. [70, 71] Kong et al. further demonstrated that the loss of mannose 6-phosphate insulin-like growth factor-2 receptor contributed to increased TGFβı levels and subsequent radiation-induced pneumonitis in patients with NSCLC.[72] In patients treated with an escalated dose of radiation, Anscher et al. reported a significant correlation between TGFβı levels and late non-pulmonary grade $\geq$ 3 radiation toxicity.[73] Despite early controversial results on its predictive value in RILT, recent studies suggested that radiation-induced elevation of plasma TGFβı at 4 weeks during the course of conventionally fractionated conformal radiation therapy is highly correlated with the occurrence of grade $\geq$ 2 RILT.[61, 74] A combined analysis of University Michigan and Peking Union of Medical College further confirmed this finding, and combining TGF-ß 1 and MLD can further stratify the risk of RILT.[75]

Of other cytokines associated with RILT, IL-1, IL-6 and IL-8 are relatively promising.[66, 67, 76-79] IL-1 (IL-1ra and IL-1β), one of the first cytokines identified, produced by macrophages, monocytes, fibroblasts and dendritic cells, forms an important part of the inflammatory response of many tissues.[80-83] IL-1β promotes inflammation in injured lung tissue,[84-86] was reported to be significantly associated with clinical RILT.[67, 87] IL-6 is a major mediator of the acute-phase inflammatory response, synthesized by a variety of cells in the lung parenchyma has increased mRNA expression in macrophages[88] and a trend toward increased plasma concentrations after thoracic RT. [63, 67] Both IL-1 and IL-6 actively participates in the inflammatory process of lymphocytic alveolitis (radiation pneumonitis) both in experimental models and in human lung diseases by stimulating inflammatory cells, particularly lymphocytes and macrophages.[79, 89, 90] IL-8, a member of the CXC chemokine family functioning as a chemoattractant, is believed to serve as a chemical signal that attracts neutrophils at the site of inflammation. serves as a chemical signal that attracts neutrophils at the site of inflammation.[91-93] Significant differences in the median values of IL-8 were observed between patients with and without symptomatic RILT.[76] Overall, plasma IL1, IL-6 and IL-8 levels may serve as a predictor for radiation pneumonitis after conventionally fractionated radiation therapy. [63, 67] Most recently, we reported that plasma level of IL-8 prior to and during conventionally fractionated radiation therapy is significantly associated with grade $\geq$ 2 RILT.[94]

Regarding genomic markers, there have been recent promising results concerning the association of single nucleotide polymorphisms (SNP) of several specific genes of white blood cells with radiation induced acute and late toxicities in other organs.[95-97] CT/CC genotypes of TGFβı rs1982073:T869C genes were associated with a lower risk of radiation pneumonitis in patients with NSCLC treated with definitive chemoradiation.[98] We have also recently demonstrated that the frequency of 7351C allele of the Tissue Plasminogen Activator (tPA, localized in the lung interstitium, associated with TGF β1 activation and increased bronchoalveolar lavage fluid albumin), was greater in patients with acute lung injury and grade ≥ 2 RILT compared with published healthy subjects data (0.73 vs. 0.68, p = 0.01) (Figure 2).[1]

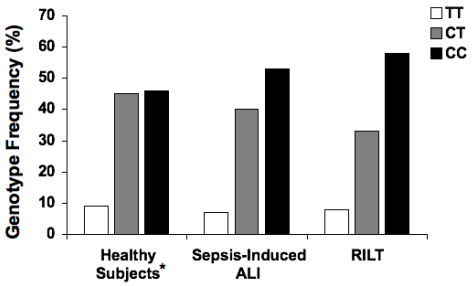


**Figure 2**: Frequency of the tPA -7351C>T genotypes in healthy subjects, sepsis-induced acute lung injury (ALI) and grade ≥ 2 radiation induced lung toxicity (RILT).[1]

There may be many other molecules involved in the processes of radiation normal tissue injury, which could be detected in the blood and serve as predictors or markers for severe pulmonary events. Recent technology advances in cytokine arrays and proteomic and genomic techniques have made it possible to evaluate many of these genes and proteins together for their association with treatment outcome. We have demonstrated that there were differential changes in proteins associated various pathways between animals sensitive to and resistant to radiation lung damage.[99] There were significant differences in at least 5 baseline plasma proteins in a study of 48 patients with and without RTIL. Using a multiplexed quantitative proteomics approach involving ExacTag labeling, RP-HPLC and LC-ESI-MS/MS, we have identified and quantified over 100 proteins from platelet poor plasma. C4b-binding protein alpha chain, complement C3 and vitronectin had significantly higher expression levels in patients with grade ≥ 2 RILT comparing to those without (Figure-3a, P<0.01).[100] Interestingly, all of these proteins are associated with inflammatory pathways; in some way interact with IL-1 ß, TNF and TGF-ß1 pathway (Figure 3b).[100]

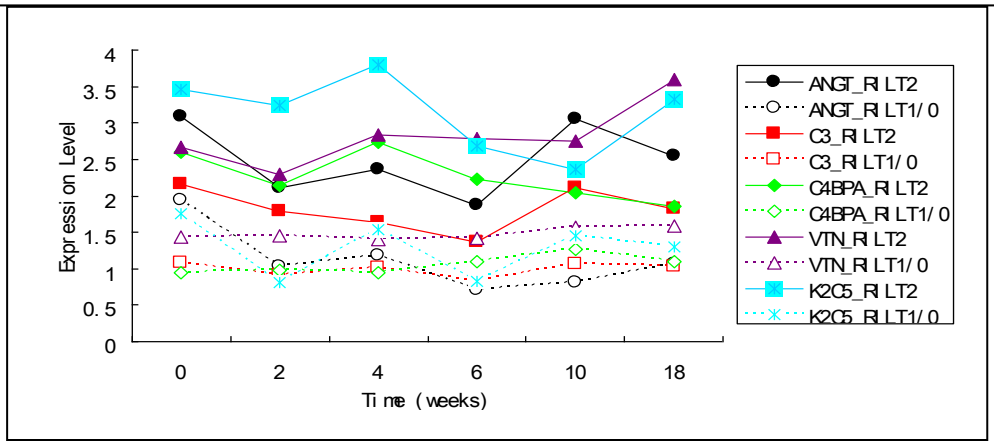


Figure 3a. Plasma Protein Expressions of patients with RILT* (RILT2) and with RILT1/0. The mean values at each time point are shown. RILT2 patients had significantly higher level of expression throughout the course of radiation and after completion of treatment. Note that these plots do not reflect data for the same set of patients, as subjects were excluded if they did not contribute at least two points to a particular protein. *RILT=Radiation-induced Lung Toxicity. AGT=Angiotensinogen, C3=Complement 3, C4BPA=C4b-binding alpha chain, VTN=Vitronectin and K5C5=Keratin/type II cytoskeletal 5.

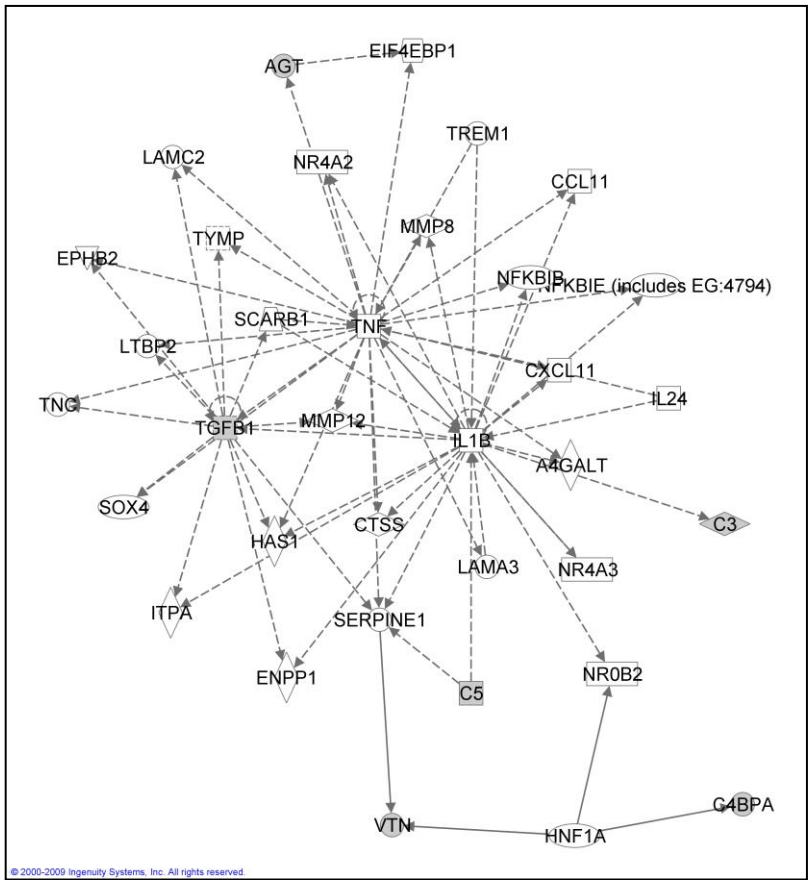


Figure 3b. Potential network of the newly identified protein markers. The markers, Complement C3 (C3), Complement C5 (C5), Angiotensinogen (AGT), Vitronectin (VTN) and C4b-binding alpha chain (C4BPA), were put on the Ingenuity pathway analysis (IPA) server with Transforming Growth Factor beta1 (TGF-β1) to generate this network. A line indicates an interaction, with the arrowhead indicating directionality. The absence of arrowheads refers to a binding interaction. The dotted line indicates an inferred or indirect interaction. This network suggests mostly indirect associations of these newly identified proteins with the function of TGF-β1, tumor necrotic factor (TNF), and interleukin-1beta (IL-1β) and pathways of inflammatory response.

**Research Plan**

Platelet-poor plasma will be obtained for cytokine and proteomic assays, serum samples will be used for metabolomics analysis. Buffy coat will be used for genomic studies. Plasma TGF-β1 will be measured by molecular specific ELISA. The levels of other plasma cytokine will be measured by LINCOplex Kit (microsphere-based sandwich immunoassay) for the concentrations of proinflammatory cytokines, including G-CSF, IL-1α, IL-1β, IL-1ra, IL-6, IL-8, IP-10, MCP-1, MIP-1, TGF-α, and TNF-α) or other advanced kit with superior performance levels when they becomes available. RILT will be diagnosed and graded based on NCI's CTCAE. The plasma proteomes will be compared using a multiplexed quantitative proteomics approach involving ExacTag labeling, RP-HPLC and LC-ESI-MS/MS. Genomic studies such as single nucleotide polymorphism (SNP) studies will be performed using polymerase chain reaction (PCR) and allele specific primers. Since this is a prospective study, we anticipate advancement in experimental technology and preliminary results, other techniques and tests will also be applied if they are found them to be superior to the above stated ones.

**Statistical Considerations**

We recognize that almost all the data of the blood marker studies discussed above were related to RILT associated with conventionally fractionated radiation therapy. In this study, we hypothesized that severe pulmonary events from hypofractionated SBRT and surgical resection have a similar mechanism to that of RILT from 3DCRT. We will use logistic models to explore the relationship between grade $\geq$ 3 pulmonary events and baseline levels of blood biomarkers of our interest (which may evolve with advances of technology and merging evidence) including (not limited to) TGFß1, IL1, IL-6, IL-8 cytokine, SNPs of these cytokines and tPA, new proteomic makers prior to and during treatment. In addition, the Generalized Estimating Equation (GEE) method will be used to explore the relationship between treatment toxicities and marker levels measured during and after treatment. For proteomic analysis, variance components models will be used to identify the differential protein expression between patients with and without grade $\geq$ 3 toxicity. Bioinformatic methodology may be applied for data analysis. As a secondary objective for toxicity study, we will also correlate blood based markers with grade $\geq$ 3 non-pulmonary toxicities, which will also be defined by CTCAE.

There will be roughly 200 patients per arm randomized for this trial, and it is expected that blood samples will be collected from nearly 100% of the registered patients. We anticipate that follow-up samples will be available from 80 to 100% of the patients. Hence, it is anticipated that a training set of 120 patients in each arm will be used for marker discovery, and validated in a test set of 80 patients in a blinded fashion.

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# 16 Appendices

## 16.1 Model Informed Consent Document

## ACOSOG Z4099/RTOG 1021: A Randomized Phase III Study of Sublobar Resection (+/- Brachytherapy) versus Stereotactic Body Radiation Therapy in High Risk Patients with Stage I Non-Small Cell Lung Cancer (NSCLC)

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family.

You are being asked to take part in this research study because you have lung cancer which may be removable with surgery. Typically this is done by removing a lobe of the lung. However, due to certain risks, you would require a surgery removing a smaller portion of the lung (a sublobar resection).

### Who is conducting this study?

This research study is being conducted by the American College of Surgeons Oncology Group (ACOSOG) and the Radiation Therapy Oncology Group (RTOG). The study doctor in charge of the study at this institution is _____ at (____) _____.

### Why is this study being done?

The purpose of this study is to compare the results of sublobar resection (removal of a small portion of a lung) with or without brachytherapy (radioactive seeds placed in the body) to stereotactic body radiation therapy (SBRT), which is radiation given by a specialized x-ray machine that targets your lung cancer. The study will compare the effects these treatments have on you and your lung cancer to find out if SBRT is as effective as sublobar resection. This study is being done because SBRT may have fewer side effects than sublobar resection, but we do not know if SBRT is as effective at preventing your cancer from returning or at prolonging your life. SBRT is the current standard treatment for patients who are not candidates for surgery.

Additional goals of this study include:

- To examine your overall health and quality of life before and after treatment
- To examine how proteins in your blood influence how you are affected by the treatment and how your tumor responds to treatment.

### How many people will take part in the study?

About 420 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.

- History and physical exam
- Pregnancy test if you are of child-bearing potential
- Tissue sampling (biopsy) of your tumor
- Lung function tests
- Combination PET and CT scan. A PET (Positron Emission Tomography) scan is a computerized image that looks at the activity of tumor cells in your entire body and that requires injection of a special marker into your vein, such as sugar (glucose) combined with a low-dose radioactive substance (a tracer). A camera records the tracer's signal as it travels through your body. A CT (Computed Tomography) scan is a study using x-rays to look at one part of your body.
- Tissue sampling (biopsy) of enlarged lymph nodes. Any lymph nodes that appear enlarged or abnormal on scans will be biopsied. Your study doctor will decide if a lymph node biopsy is needed.

**After you join the study...**
You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your study doctor can choose the group you will be in. You will have an equal chance of being placed in either group.

**If you are in Group 1 (often called "Arm 1"):** You will receive sublobar resection with or without brachytherapy.

**If you are in Group 2 (often called "Arm 2"):** You will receive stereotactic body radiation therapy.

By the time enrollment to the study is finished, there will be a roughly equal number of people in each group.

**Before you start treatment...**
You will need to have the following exams, tests or procedures:

- Questionnaires about your health and quality of life. The questionnaires would be used to examine your health and quality of life before and after treatment, and any changes that occur. The questionnaires each take about 5 minutes to complete.

You also may volunteer to donate tissue (for patients receiving surgery) and blood specimens for use in correlative science studies. Correlative science studies are additional studies being done as part of the treatment study. They are for research purposes only. You may still participate in the treatment study if you say "no" to participating in these extra studies. You also may volunteer to

donate leftover blood samples and tissue samples for use in future studies. More information about the optional sample donation is provided in a later section of this form.

**During study therapy...**

A. If you are randomized to the "sublobar resection with or without brachytherapy" group:
You and your study doctor will decide in advance whether brachytherapy should be used or not. Then you will have surgery, where your study doctor will remove a portion of your lung containing the lung cancer. If you and your study doctor decide to use brachytherapy, after removing the tumor your study doctor will work with your radiation oncologist to place some radioactive seeds on the edge of the cut portion of lung. These seeds will deliver a low dose of radiation to the lung as an additional measure to prevent the cancer from coming back. If you and your study doctor decide against using brachytherapy, your study doctor will not place any seeds after removing the tumor.

We do not know if the addition of brachytherapy is more effective than surgery alone. Other research studies are examining this question, but those results are not yet available (except for the side effect information listed in the Risks section of this form). It will be up to you and your surgeon to decide whether brachytherapy should be used.

B. If you are randomized to the "stereotactic body radiation therapy (SBRT)" group:
You will receive radiation treatment on 3 separate visits, each visit occurring 2 to 8 days apart. The radiation therapy at each visit will take 20-60 minutes. Before starting SBRT, you will have a "planning" CT scan, which provides accurate images for your radiation oncologist to help him or her aim the radiation. The radiation therapy will be directed at your tumor using a 3-dimensional system that allows for more accurate targeting of the tumor than conventional radiation. You will lie in a specific position, possibly within a frame device or on a large plastic bag filled with tiny foam balls similar to a bean bag. The purpose of the frame or bag is to hold your body as still as possible for planning and treatment. After you are positioned, the study doctor will check your breathing and see how your organs move. The study doctor will try to limit the effect of that movement on the position of your tumor by timing your breathing. The study doctor may use a device to control the depth of your breathing or one to monitor the rate and pattern of your breathing so that the radiation can be delivered to the tumor while accounting for the effect of breathing. All treatment will be completed within 16 days.

Stereotactic body radiation therapy (SBRT) is a newer radiation treatment that gives fewer but higher doses of radiation than standard radiation. It uses special equipment to position the patient and guide focused beams toward the cancer and away from normal surrounding lung tissue. The higher dose technique may work better to kill cancer cells potentially with fewer side effects than standard radiation therapy

**After study therapy...**

You will see your study doctor at 4 weeks, every 3 months for 2 years, every 6 months for 1 year and then yearly until 5 years total. At those visits you will have the following tests.

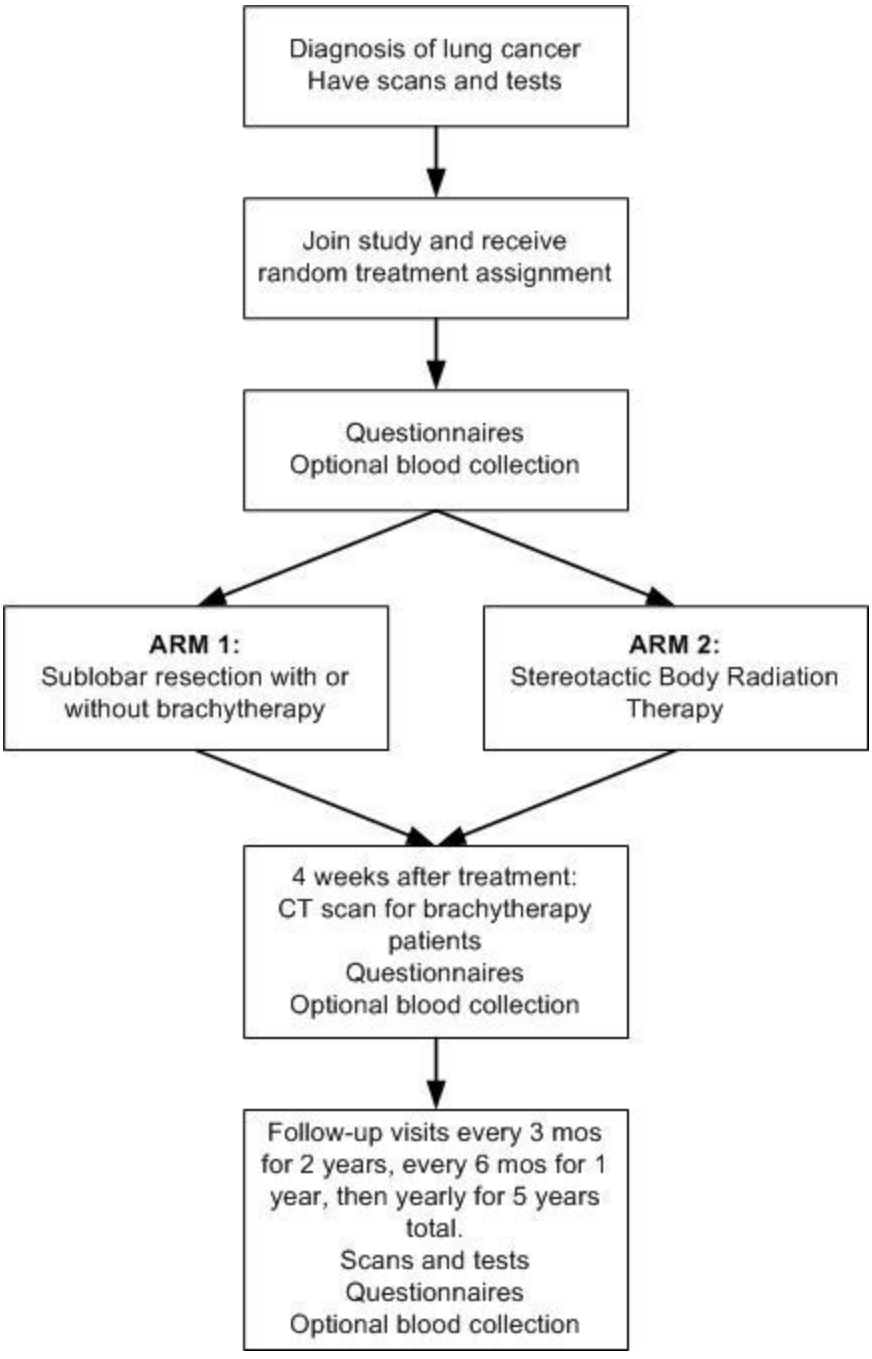
- History and physical exam

- CT scan or combination PET/CT scan of chest and upper abdomen. A CT scan will be done at all visits. The CT scan will include a PET scan at 6 months, 12 months, and then yearly. A CT scan will be done at 4 weeks after treatment only for participants who received brachytherapy seeds at surgery.
- Lung function tests (at 3 months, 6 months, 12 months and 24 months)
- Questionnaires about your health and quality of life (at 4 weeks, 3 months, 6 months, 12 months and 24 months)

Copies of images and reports from the scans conducted before and after treatment may be submitted for review by study personnel. This is done to make sure the scans are of good quality. Only your patient study number and initials will appear on the reports, images and accompanying paperwork. No other identifying information will be included. The images and reports will be stored in a secure password-protected database.

## Study Plan

Another way to find out what will happen to you during the study is to read the study plan below. Start reading at the top and read down the list, following the arrows.




## How long will I be in the study?

You will be in the study for about 5 years. You will have surgery or SBRT, and then you will see your study doctor at 4 weeks, every 3 months for 2 years, every 6 months for 1 year, then yearly until five years total.

There may come a time when your study doctor may decide to take you off study even though you want to continue to participate. This may happen if:

- You are unable to meet the ongoing requirements of the study;
- Your medical condition changes and it is no longer appropriate for you to participate;
- ACOSOG finds it must stop the study.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to your study doctor first.

## 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 surgery or radiation therapy can be evaluated by your study doctor. Another reason to tell your study 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 are the risks of the study?

While on the study, you are at risk for these side effects. You should discuss these with your study doctor. There also may be other side effects that we cannot predict. Drugs may be given to make the side effects less serious and uncomfortable. Many side effects go away shortly after the radiation therapy is stopped, but in some cases side effects can be serious or long-lasting or permanent. There is also a risk of death.

**Risks and side effects related to surgery include those that are:**

**Likely**:

- Prolonged chest tube drainage after your lung surgery
- Persistent cough or trouble breathing that may require further medical treatment
- Shortness of breath

**Less Likely:**

- Lung infection/pneumonia
- Pulmonary embolus (a blood clot in the lung)
- Deep vein thrombosis (DVT - a blood clot in a large vein; such a blood clot can cause a stroke or a heart attack in some cases)
- Prolonged intubation or reintubation after lung surgery (this means that a tube placed in your airway to help you breath during the surgery may need to be left in for longer than 24 hours after surgery is finished, or may need to be placed in your airway again after it is initially taken out).

- Wound infection
- Bronchopleural fistula (leakage of air from the remaining lung after your lung cancer has been removed)
- Injury to laryngeal nerves (this may cause hoarseness or difficulty swallowing)
- Changes in lung function tests

**Rare but Serious:**

- Sepsis (a severe form of infection)
- Cardiac ischemia/infarction (heart attack)
- Irregular or rapid heartbeat that may be associated with heart attacks
- Adult respiratory distress syndrome (severe inflammation of the lung that affects the ability to breath normally)
- Injury to a blood vessel that can result in heavy bleeding (or hemorrhage) during or after your operation.

**Risks and side effects related to brachytherapy include those that are:**

**Likely:**

- Lung infection/pneumonia
- Adult respiratory distress syndrome (severe inflammation of the lung that affects the ability to breath normally)
- Shortness of breath

**Less Likely:**

- Pleural infection (infection of the area around the lung)
- Bronchopleural fistula (leakage of air from the remaining lung after you lung cancer has been removed)
- Radiation affecting other people (there is a small possibility that the radiation from the seeds can affect a person close by you)
- Delay in wound healing

**Additional risks seen in patients who were treated on a previous study of surgery and brachytherapy:**

- Urinary tract infection or other infections
- Hypoxia (condition in which there is a decrease in the oxygen supply to a tissue)
- Atrial fibrillation (irregular heart beat)
- Hypotension (low blood pressure), which may cause fainting
- Dehydration (lack of fluids in the body)

**Risks and side effects related to stereotactic body radiation therapy include those that are:**

**Likely:**

- Damage to surrounding normal lung and/or collapse of a portion of treated lung
- Changes in the lungs as the tumor shrinks. These changes will be recognized by your study doctor on your x-rays or scans as expected "scarring" that is developing. In most patients, no noticeable symptoms will result from this lung damage.
- Fatigue
- Redness of irritation of the skin in the treatment area
- Hair loss in the treatment area (chest hair)
- Some soreness of the ribs with an increased risk of rib fracture. Treatment for such symptoms usually consists of rest, heat, and pain medication.
- Damage to the bronchus (airways in the lungs)

**Less Likely:**

- Cough
- Increased phlegm production
- Difficulty breathing
- Fever
- Changes in lung function tests

**Rare but Serious:**

- Some patients can have the following symptoms associated with lung scarring: shortness of breath, cough, fever, and/or pain in the chest wall. These patients may require oxygen for a short time or permanently. Lung damage can be life threatening.
- Damage to the lining of the heart, which can cause fluid accumulation around the heart and chest pain, shortness of breath, and/or irregular or rapid heart beat
- Damage to the heart muscle, which can cause heart attack, heart failure, or death
- Damage to the spinal cord, which can cause numbness, weakness, tingling, and/or inability to use the arms and/or legs
- Damage to the esophagus, which can cause problems with swallowing
- Damage to the large blood vessels surrounding the heart, which could cause coughing up of blood and possibly death
- Severe pain in the treatment area
- Severe skin damage in the treatment area leading to an open wound

During the process of treatment planning and radiation, you will lie in a specific position, possibly within a frame device, and some patients can become claustrophobic. Medications can be given to make you feel more comfortable should this happen. Also, your study doctor may give you pain medication before each treatment to decrease any discomfort you may have due to lying on a hard surface and/or due to lying with your arms held above your head during the treatment.

**Reproductive risks:** You should not become pregnant or father a baby while on this study because the treatment in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

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

## Are there benefits to taking part in the study?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the study will help us determine if SBRT is as effective as sublobar resection in treating lung cancer. We hope the information learned from this study will benefit other patients with lung cancer in the future.

## What other options are there?

Instead of being in this study, you have these options:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment

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

## What about confidentiality?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The American College of Surgeons Oncology Group (ACOSOG);
- The Radiation Therapy Oncology Group (RTOG);
- The ACOSOG Data Monitoring Committee, a group of experts who regularly review the progress of the study;
- The local Institutional Review Board (IRB), a group of people at this institution who review the research study to protect your rights;

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA) and the Office for Human Research Protection (OHRP), involved in keeping research safe for people;
- The Quality Assurance Review Center (QARC). QARC is an organization funded by the National Cancer Institute (NCI) to provide expert review of radiation treatment and diagnostic imaging data;
- The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials;
- Other cancer research groups who endorse this study.

## What are the costs?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan/insurance company or the hospital billing representative to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment. You will not have to pay for any of the costs related to the research aspects of this study (for example, extra blood or tissue sampling, and the quality of life or other questionnaires).

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. You or your insurance company will be charged for continuing medical care and/or hospitalization.

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

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

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

## What are my rights as a participant?

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 this 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.

## Tissue and Blood Sample Donation for Research

The next section of the consent form is about optional tissue and blood sample donation for correlative science studies. Correlative studies are additional studies being done as part of the treatment study. They are for research purposes only. You may still participate in the treatment study if you say "no" to participating in these extra studies.

**Tissue Samples**

If you are randomized to receive surgery, we would like to collect tissue samples from the tumor that is removed at your surgery. These tissue samples would be stored for future studies.

**Blood Samples**

If you agree, blood would be collected at the following time points. Before surgery or SBRT, 3 tubes (about 6 teaspoons) would be collected. At the other time points, 2 tubes (about 4 teaspoons) would be collected.

- Before surgery or SBRT. For patients receiving surgery, the blood may be drawn at the time of surgery if you prefer.
- 4 weeks after surgery (for patients receiving surgery)
- Before the last SBRT treatment (for patients receiving SBRT)
- Every 6 months for 2 years, then yearly until 5 years total

These blood samples would be used to examine how molecular differences in your tumor (called "tumor markers") and proteins in your blood affect how your tumor responds to treatment.

ACOSOG would also like to keep any blood specimens left over from this current study and the tissue specimens for future research. If you agree, these specimens will be kept by ACOSOG and may be used in research to learn more about cancer and other diseases. You can learn more about how biological specimens are used for research at www.cancer.gov.

## About Using Biological Specimens for Research

Your blood samples and your tissue samples are called "biological specimens."

## Things to Think About

The choice to let ACOSOG collect the specimens is up to you. No matter what you decide to do, it will not affect your care.

Even if you decide now that your specimens can be collected for research, you can change your mind at any time. Just contact your study doctor and let them know that you do not want your biological specimens used for research. Any sample that remains will either be destroyed (in the case of blood or certain other tissue samples) or returned to the hospital where you had your treatment, and will no longer be used for research. You will not have access to your samples and we cannot return them directly to you. Also, there are some things that cannot be changed, stopped, or returned such as samples already given to researchers or used in research studies or research results that used your samples and related information.

In the future, people who do research may need to know more about your health. While reports about your health may be given to the researchers, any other information that will let the researchers know who you are (such as your initials, birthdate or medical record number) will not be given under any circumstances.

Your specimens will be used only for research and will not be sold for profit. However, the research done with your tissue may help to develop new products in the future, but you will not be able to benefit financially from any of these.

## Genetic Research

Sometimes specimens are used for genetic (DNA) research.

The purpose of doing genetic research is to discover changes in genes (or DNA) associated with the development or outcome of cancer. This could lead to better ways to prevent, detect, and treat cancer and, perhaps, other diseases as well. Due to advances in the techniques and tests used to analyze genetic material in specimens (DNA), it is likely that your specimens could be used for this type of research, if you agree.

Body tissues are made up of cells. Cells contain DNA, which is part of your unique genetic material that carries the instructions for your body's development and function. DNA can be analyzed so that your unique, exact genetic code or the altered genetic code of your tumor cells can be identified and compared to other patients. Cancer can result from changes in a person's genetic material (DNA) that causes cells to divide in an uncontrolled way and, sometimes, to travel to other organs. Currently, researchers and doctors know some of the genetic changes that can cause cancer, but they do not know all of the genetic changes that can cause cancer.

By studying the genetic code of cancer cells and the people who have cancer, scientists expect to identify most of the genetic changes associated with different kinds of cancer. ACOSOG and scientists who work with ACOSOG members, such as your study doctor, would also like to compare genetic information obtained from you biological specimens (e.g. blood and cancer tissue) with information available from your progress on the ACOSOG study, such as the response to treatment and your long term health. With this knowledge, future treatments for cancer could become customized to a patient's unique genetic make-up (this is known as personalized medicine).

Your tissue samples, blood samples and medical information collected as part of the ACOSOG study will be labeled with a code.

Only ACOSOG will have the information that matches the code to traditionally-used identifying information, such as your initials, birthdate or medical record number. ACOSOG will keep the information that matches the code to this traditionally-used identifying information in a safeguarded database. Only very few, authorized people, who have specifically agreed to protect your identity, will have access to this database. All other researchers and personnel, including those who will be working with your samples and medical information, will not have access to any of the traditionally-used identifying information about you.

Information from analyses of your coded samples and your coded medical information will be put into databases along with information from other research participants. These databases will be accessible by the Internet. The purpose of making sequence and medical information available is so that they can be used by scientific researchers throughout the world to study cancer and other diseases.

Please note that traditionally-used identifying information about you, such as your initials, birthdate or medical record number would NOT be put into the databases.

Even if your specimens are used for this kind of research, the results will not be put in your health records and although you can learn more about this type of research, individual information about your genetic code or your tumor will not be available to you.

## Benefits

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

## Risks

- Your privacy is very important to us and we will use many safety measures to protect your privacy. However, in spite of all of the safety measures that we use, it is impossible to guarantee that links between you and the genetic information we would obtain will never become known. Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other relatives. Consequently, it may be possible that genetic information from them could be used to try and identify your sample from the publicly available information. Similarly, it may be possible that genetic information from you could be used to help identify them.
- While the databases used to store your genetic information would not contain information that is traditionally used to identify you, such as your initials, birthdate or medical record number, people may develop ways in the future that would allow someone to link your genetic or medical information in our databases back to you.

  We would like to emphasize that we will do everything we can to protect your private information. However because of the nature of the issues, we feel that we should explain these issues to you carefully.
- An additional risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

## Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No".

**If I choose to join the study:**

1. My blood specimens may be collected for use in this study.

Yes No

2. My blood specimens may be kept for use in future research to learn about, prevent, or treat cancer.

   Yes No

3. My blood specimens may be kept for use in future research to learn about genetics and how they relate to cancer. This may also include research on inherited traits (genes passed on in families).

   Yes No

4. My blood specimens may be kept for use in future research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease). This may also include genetic research on inherited traits (genes passed on in families).

   Yes No

**If I am randomized to receive surgery:**

5. My tissue specimens may be kept for use in future research to learn about, prevent, or treat cancer.

   Yes No

6. My tissue specimens may be kept for use in future research to learn about genetics and how they relate to cancer. This may also include research on inherited traits (genes passed on in families).

   Yes No

7. My tissue specimens may be kept for use in future research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease). This may also include genetic research on inherited traits (genes passed on in families).

   Yes No

## Whom do I call if I have questions or problems?

For questions about the study or a research-related injury, contact the researcher *NAME(S)* at *TELEPHONE NUMBER*.

For questions about your rights as a research participant, contact the *NAME OF CENTER* institutional review board (which is a group of people who review the research to protect your rights) at *TELEPHONE NUMBER*. *[and, if available, list patient representative (or other individual who is not on the research team or IRB).]*

## Where can I get more information?

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

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

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

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

## Signature

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

**Participant's Signature _____ Date _____**

## 16.2 Staging Reference (AJCC Cancer Staging Manual, 7th Edition, 2010)

| | |
|---|---|
| **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)* |
| **T1a** | Tumor 2 cm or less in greatest dimension |
| **T1b** | Tumor more than 2 cm but 3 cm or less in greatest dimension |
| **T2** | Tumor more than 3 cm but 7 cm or less or tumor with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less):<br>• Involves main bronchus, 2 cm or more distal to the carina<br>• Invades visceral pleura (PL1 or PL2)<br>• Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung |
| **T2a** | Tumor more than 3 cm but 5 cm or less in greatest dimension |
| **T2b** | Tumor more than 5 cm but 7 cm or less in greatest dimension |
| **T3** | Tumor more than 7 cm or one that directly invades any of the following: parietal pleura (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (less than 2 cm distal to the carina* but without involvement of the carina); or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe |
| **T4** | Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe |
| **Nodal Involvement (N)** | |
| **NX** | Regional lymph nodes cannot be assessed |
| **N0** | No regional lymph node metastases |
| **N1** | Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension |
| **N2** | Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s) |
| **N3** | Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s) |
| **Distant Metastasis (M)** | |
| **MX** | Distant metastasis cannot be assessed |
| **M0** | No distant metastasis |
| **M1** | Distant metastasis |
| **M1a** | Separate tumor nodule(s) in a contralateral lobe, tumor with pleural nodules or malignant pleural (or pericardial) effusion** |
| **M1b** | Distant metastasis |

* 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

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

## 16.3 Stage Grouping

| Stage | TNM |
|---|---|
| **IA** | T1a N0 M0 |
| | T1b N0 M0 |
| **IB** | T2a N0 M0 |
| **IIA** | T2b N0 M0 |
| | T1a N1 M0 |
| | T1b N1 M0 |
| | T2a N1 M0 |
| **IIB** | T2b N1 M0 |
| | T3 N0 M0 |
| **IIIA** | T1a N2 M0 |
| | T1b N2 M0 |
| | T2a N2 M0 |
| | T2b N2 M0 |
| | T3 N1 M0 |
| | T3 N2 M0 |
| | T4 N0 M0 |
| | T4 N1 M0 |
| **IIIB** | T1a N3 M0 |
| | T1b N3 M0 |
| | T2a N3 M0 |
| | T2b N3 M0 |
| | T3 N3 M0 |
| | T4 N2 M0 |
| | T4 N3 M0 |
| **IV** | Any T Any N M1a |
| | Any T Any N M1b |

## 16.4 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.

## 16.5 Cancer Trials Support Unit (CTSU) Participation Procedures

| To submit site registration documents: | For patient enrollments: | To submit study forms or data: |
|---|---|---|
| CTSU Regulatory Office<br>1818 Market Street, Suite 1100<br>Philadelphia, PA 19103<br>Phone: 1-888-823-5923<br>Fax: 215-569-0206 | See Section 4.0. | See Section 9.0. |
| For patient enrollments that must be completed within approximately one hour or for extenuating circumstances, call 301-704-2376.<br>For all other CTSU patient enrollments, please use 1-888-462-3009.<br>**No exemptions or waivers will be granted for patients who do not meet the eligibility criteria.** | | |
| **For all protocol questions:**<br>Contact the ACOSOG QA Specialist. | | |
| **The CTSU Web site is located at: http://www.ctsu.org.** | | |

### 16.5.1 Registration and Randomization

Registration is available 24 hours a day via the CTSU's Oncology Patient Enrollment Network (OPEN) Portal system. All participating sites (ACOSOG and non-ACOSOG sites) will use OPEN to enroll patients to this study. See Section 4.0.

### 16.5.2 Other Protocol Requirements

CTSU sites will follow the requirements of the protocol for all required procedures and submissions.