A Phase II Randomized Study of 2 Stereotactic Body Radiation Therapy (SBRT) Regimens for Medically Inoperable Patients with Node Negative, Peripheral Non-Small Cell Lung Cancer

Protocol #: I 124407

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Network Investigator Signature Page

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PROTOCOL APPROVAL AND INVESTIGATOR AGREEMENT
I have read and familiarized myself with this protocol and I agree to conduct the study as described according to GCP and ICH guidelines.

Principal Investigator

_____ _____
Signed Date

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Printed

Address: _____

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Phone: _____

Fax: _____

E-mail: _____

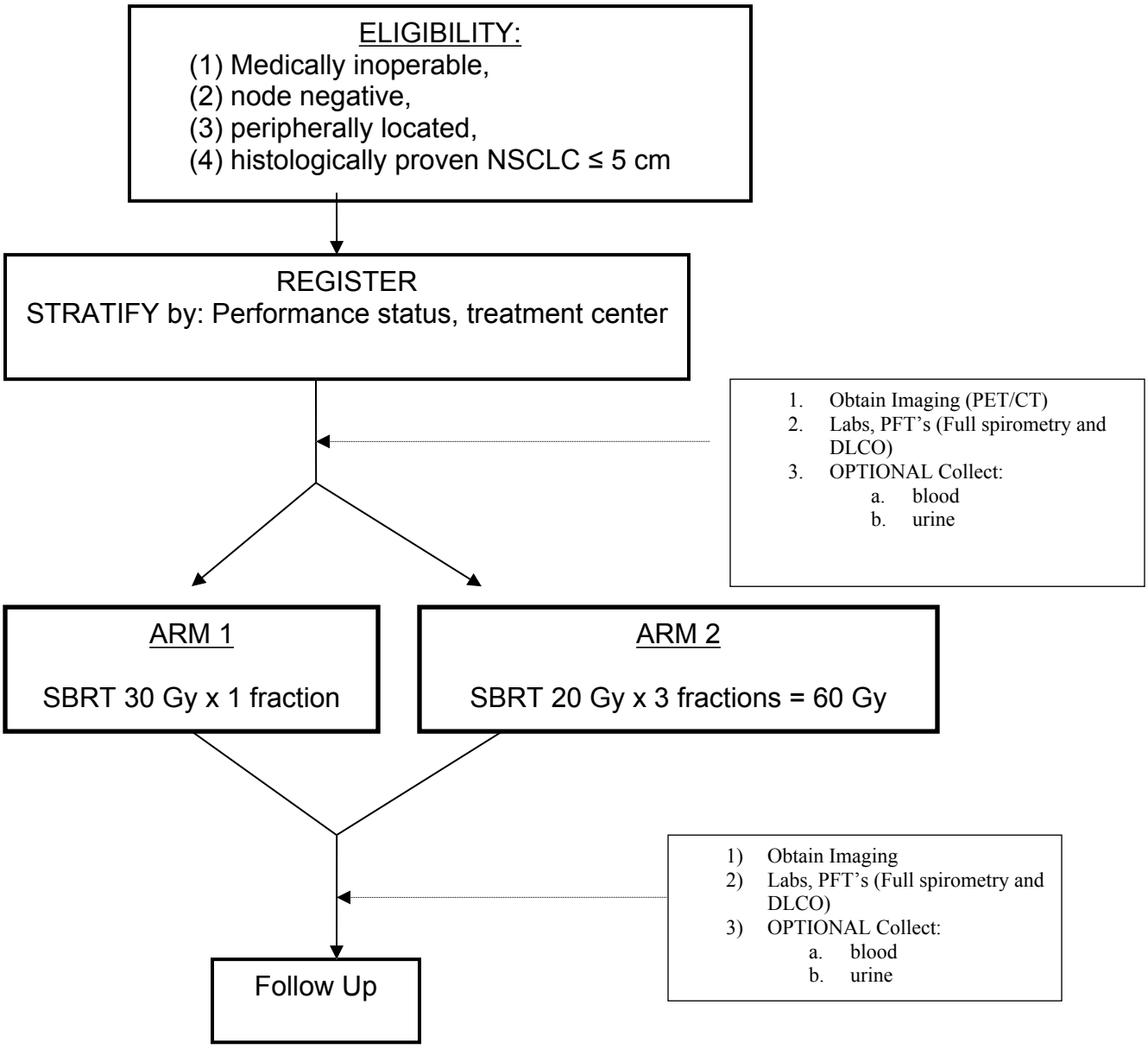
NOTE: Please see Appendix III for Network-specific instructions that will apply to your site.

ABSTRACT

- **Principal Investigator**: Anurag K. Singh, M.D.
- **Co-Investigators:** Heinz Baumann, PhD; Todd Demmy, MD; Jorge Gomez, MD; Dominick Lamonica, MD; C.E. Nwogu, MD; Harish Malhotra, PhD; Austin Miller, PhD; Sai Yendamuri, MD and Hua Zhao, PhD
- **Phase: II Randomized**
- **Objectives:** To determine the incidence of RTOG grade 3 or higher toxicity with 2 different radiation therapy regimens.
- **Treatment Overview:** Randomized between 30 Gy once or 20 Gy x 3.
- **Eligibility Criteria:** Medically inoperable patients with node negative, peripherally located, histologically proven NSCLC ≤ 5 cm are eligible.
- **Subjects and target study duration:** The trial will accrue 98 patients over 12 years.
- **Endpoints:** Incidence of RTOG grade 3 or higher toxicity, overall survival, correlations between blood and serum markers and survival and toxicity.
- **Statistics:** This is a phase II randomized study to compare incidence of RTOG grade 3 or higher toxicity associated with 2 different, established SBRT regimens for NSCLC. Group sample sizes of 49 in group one (Gy x 3) and 49 in group two (Gy x 1) achieve 81% power to detect a difference between the group incidences of toxicity of 0.17. The incidence of toxicity in group one (the treatment group) is assumed to be 0.03 under the null hypothesis and 0.2000 under the alternative hypothesis. The proportion in group two (the control group) is 0.03. The test statistic used is the one-sided Z test with continuity correction and unpooled variance. The significance level of the test was targeted at 0.05. The significance level actually achieved by this design is 0.0037.

  Descriptive statistics will be presented for each group. Incidence of toxicity will be compared using Z test. Disease free survival and overall survival will be compared between two groups using log-rank test statistics. Correlation analysis will be performed to explore the relationship between outcomes and toxicities with tumor biomarkers. The estimate of acute and long term toxicity associated with SBRT for NSCLC will be reported.

SCHEMA


ELIGIBILITY:
(1) Medically inoperable,
(2) node negative,
(3) peripherally located,
(4) histologically proven NSCLC ≤ 5 cm
REGISTER
STRATIFY by: Performance status, treatment center
1. Obtain Imaging (PET/CT)
2. Labs, PFT's (Full spirometry and DLCO)
3. OPTIONAL Collect:
a. blood
b. urine
ARM 1
SBRT 30 Gy x 1 fraction
ARM 2
SBRT 20 Gy x 3 fractions = 60 Gy
1) Obtain Imaging
2) Labs, PFT's (Full spirometry and DLCO)
3) OPTIONAL Collect:
a. blood
b. urine
Follow Up

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1.0 BACKGROUND and RATIONALE

Lung cancer remains the leading cause of cancer death with an estimated 213,380 new cases diagnosed in 2007 with 160,390 deaths[1]. Approximately 75% of lung cancers are non-small cell lung cancer (NSCLC) and 15-20% of NSCLC patients are diagnosed with localized disease[1]. With improved screening, the percent of patients diagnosed with localized disease is expected to rise[2].

Surgery is the mainstay of treatment for localized NSCLC with favorable 5 year survival rates of 65-70%[3]. However, NSCLC often occurs in patients with compromised lung function. Thus, many patients with localized disease are termed medically inoperable[4].

Radiation using conventional techniques has been used extensively[5, 6]. However, outcomes have been inferior to surgery alone. Rates of 5 year survival with definitive RT have ranged from 10-30%[6-9], well inferior to rates of 65-70% achieved with surgery alone[3, 10].

Many factors have been suggested to explain this discrepancy in outcomes. Notably, cause-specific survivals are 10-20% higher than overall survivals in medically inoperable patients due to mortality from competing causes[8, 9, 11, 12]. Additionally local failures, up to 85% biopsy proven[13], have continued to be a problem following curative radiation therapy.

High rates of local failure have spurred several trials in dose escalation with conventional fractionation. Several have shown improved outcomes with higher doses [9, 14-18]. However, not all series have shown improved survival with higher doses[11, 19].

Such mixed results and overall suboptimal outcomes with conventional fractionation have prompted evaluation of alternate fractionation schemes[17, 20, 21]. Alternate fractionation schemes employing conventional treatment margins have shown significantly increased toxicity[20].

Efforts to increase the dose per fraction to the tumor while limiting the dose to surrounding normal tissues has lead to the development of stereotactic body radiation therapy (SBRT.) SBRT used has been the topic of a growing number of single institution and cooperative group studies[22-25].

1.1 Sterotactic Body Radiation Therapy (SBRT)

As shown below, SBRT has been shown to have excellent results and low toxicity with either single or multiple fraction schemes. The data suggest that 30 Gy in a single fraction is superior to doses less than 30 Gy. For

multiple fraction schemes, 20 Gy times 3 fractions appears to be a safe and effective dose.

1.1.1 Multiple Fraction SBRT (for peripheral lesions)
Onishi et al. reported outcomes among 257 patients treated in 14 Japanese centers with SBRT using many dosing schemes (1-22 fractions at 3-12 Gy per fraction). Total dose ranged from 18 to 75 Gy. With 38 months median follow-up, patients receiving a biologically equivalent dose (BED) of >100 Gy experienced fewer local recurrences than those patients receiving < 100 Gy BED (42.9 vs 8.1%, p<0.001.) Similarly, survival was significantly improved with higher BED doses, 70.8 vs. 30.2% (p<0.05.) grade 3 or higher toxicity was observed in 5.4% [26].

Echoing these results, Wulf et al. studied the dose-response for local tumor control after SBRT in 92 pulmonary tumors (36 NSCLC and 56 metastases.). Short course irradiation of 1-8 fractions with different fraction doses was used. After a median follow-up of 14 months (2-85 months) 11 local recurrences were observed. A BED dose of 94Gy at the isocenter and 50Gy at the PTV-margin were demonstrated to give 50% probability of tumor control (TCD50). Multivariate analysis revealed the dose at the PTV-margin as the only significant factor for local control. No severe toxicity was observed[27].

While the initial experience with multi-fraction SBRT regimens as summarized above showed very little toxicity, more recent publications have shown higher rates of toxicity, likely somewhat secondary to more rigorous reporting of toxicities in more recent trials.

Baumann et al. reported on 138 patients with stage I NSCLC treated with SBRT delivered using a 3D conformal multifield technique and a stereotactic body frame. Doses delivered were 30-48 Gy (65% isodose at the periphery of PTV) in 2-4 fractions. Equivalent dose in 2 Gy fractions (EQD2) was in the range of 50-100 Gy. Three- and 5-year overall survival was 52 and 26% respectively. Lung cancer specific 3- and 5-year overall survival was 66 and 40% respectively. EQD2 (> vs <55.6 Gy) showed a statistically significant survival benefit for the higher doses. Fifty nine percent (83/138) of the patients had no side effects. Fourteen patients (10%) experienced RTOG grade 3-4 toxicity[28].

1.1.2 Multiple Fraction SBRT (the Indiana Univiersity Experience)
Investigators at Indiana University conducted a Phase I study among 47 patients with Stage IA or IB NSCLC. The study began at a dose of 8Gy in 3 fractions and escalated to a dose of 24 Gy in 3 fractions. Significantly decreased rates of LR (only 1 of 9) were noted among patients receiving >16 Gy per fraction. No significant toxicities were reported at 20 Gy per fraction. The maximum tolerated dose was realized at 72 Gy for tumors

larger than 5 cm. Dose-limiting toxicity included bronchitis, pericardial effusion, hypoxia, and pneumonitis [29].

Timmerman et al. carried out a prospective, phase II, 70 patient trial using stereotactic body radiation therapy (SBRT) to doses of 60 to 66 Gy in three fractions during 1 to 2 weeks. With a median follow-up of 17.5 months, the 3-month major response rate was 60%. Kaplan-Meier local control at 2 years was 95%. Grade 3 to 5 toxicity occurred in a total of 14 patients. Six patients died as a consequence of treatment related toxicity. Median overall survival was 32.6 months and 2-year overall survival was 54.7%. Among patients experiencing toxicity, the median time to observation was 10.5 months. Tumors with GTV volume of more than 10 mL had an eight-fold risk of high-grade toxicity compared with smaller tumors (P = .017). Patients treated for tumors in the peripheral lung had 2-year ***freedom from severe toxicity*** of 83% compared with only **54%** for patients with **central tumors[30].**

Based on the early experience from Indiana University[31], the Radiation Therapy Oncology Group (RTOG) opened a prospective trial of SBRT in 2004 (RTOG study 0236.) This study enrolled 52 medically inoperable patients with peripherally located, node negative NSCLC measuring ≤5cm. Patients received three 20 Gy fractions over 10-14 days. The trial was closed to accrual in October 2006. Early results in abstract form show 15% grade 3-4 toxicity. Specifically, with median follow-up of 8.7 months, there was one (2%) grade 4 and 7 (13%) grade 3 pulmonary/upper respiratory adverse events reported as related to protocol treatment. Two of the 7 pts reported pulmonary function test decreased, 1 pt reported cough/dyspnea, 1 pt reported hypoxia, 1 pt reported pneumonitis, 1 pt reported cough/forced expiratory volume, and 1 pt reported pneumothorax. There was also a grade 3 dermatitis and a grade 3 syncope reported as related to protocol treatment. No treatment related deaths have been reported[32]. As the median time to toxicity was previously reported to be 10.5 months in the previous Timmerman publication[30], the observed toxicity reported in this RTOG abstract (with only 8.7 months of follow-up) can be expected to rise.

1.1.3 Single Fraction SBRT (for peripheral lesions)

Hof et al. reported outcomes among 42 patients with stage I or II NSCLC treated with single dose SBRT (dose range 19-30 Gy.) With a median follow-up of 15 months, overall survival and disease free survival at 12, 24, and 36 months were 74.5%, 65.4%, 37.4% and 70.2%, 49.1%, and 49.1% respectively. Local tumor control was 89.5%, 67.9%, and 67.9% at the same time points. Local tumor control was significantly improved in those patients receiving 26-30 Gy (n=32) versus lower doses (p=0.032)[33]. Regarding toxicity, follow up CT scan normal tissue changes (including pneumonitic changes and fibrosis) were noted in the treatment area in

64.3% of patients. However, no CTC grade 3 or 4 toxicities were noted. Minor cough and slightly increased dyspnea were the only clinical toxicities observed.

Hara et al reported outcomes among 59 patients with malignant lung tumors (11 primary lung tumors, 48 metastases) treated for localized disease within the lung or metastatic disease to the lung and noted one and two year local progression free rates of 93 and 78%. All patients were treated with single dose SBRT and improved local control was noted among patients receiving >30 Gy versus 26-30 Gy (9 patients.) Local regrowth of the irradiated tumor was a direct cause of death in two patients. Only the minimal radiation dose to the reference target volume tended to have an influence on the LPFR (P = 0.068). RTOG Grade 3 respiratory symptoms were noted in one patient[34].

1.1.4 Rationale for the Current Study Design

From the aforementioned studies, we can conclude that single fraction and multi-fraction SBRT regimens are feasible and yield excellent local control. Most studies have used the multi-fraction regimen and no prior study has compared the two regimens in terms of efficacy and toxicity.

With multi-fraction regimens, the severe toxicity of 17% for those with peripheral lesions reported by Indiana University[30] is greater than suggested by the data summarized in section 1.1.1, which includes previous data from Indiana. For this reason, even in patients with peripheral lesions, it is imperative that SBRT be performed in the setting of a clinical trial (as opposed to routine clinical practice) so that the true incidence of toxicity can be captured and reported.

Of interest, no studies have yet shown major toxicity with single fraction regimens of 30 Gy. However, toxicities have been more rigorously monitored and reported in studies of multi-fraction regimens.

Given excellent reported control rates for both regimens, and absent any significant reported toxicity for single fraction therapy, a comparison of 30 Gy in one fraction versus 60 Gy in 3 fractions is warranted. Comparison of these regimens via a randomized prospective trial will allow for collection of a wealth of valuable information including, but not limited to, toxicity, outcomes, cost, patient comfort, and radiobiologic and dosimetric comparisons.

Interestingly, the Radiation Therapy Oncology Group (RTOG,) has chosen not to pursue single fraction regimens. Even, for central lesions where toxicity is high with the RTOG's preferred 20 Gy x 3 regimen, currently planned studies hope to reduce toxicity by increasing the number of fractions and reducing dose. A similar strategy appears to taking hold in

Japan. Certainly, reimbursement is less for a single fraction treatment and the effect of this variable is difficult to ascertain. Only in Germany does there appear to be interest in single fraction regimens. Consequently, it appears unlikely that many other institutions would be interested in the study design proposed here.

1.2 Predictors of Outcomes (Imaging, Biomarkers, etc)

Although studies have demonstrated improved outcomes among patients treated with SBRT versus conventional techniques, patients continue to fail and some experience significant toxicity.

A well delineated, uniformly staged, and followed prospective cohort would be invaluable at interrogating and validating known predictors of toxicity and outcome. Also, analysis of data from such a cohort may identify novel predictors of outcome following SBRT.

Additionally, serial PFTs, imaging data, dosimetry data, blood and urine samples will be collected for these analyses .

The study team members will perform clinical data collection and utilize the RPCI Data Bank and BioRepository (DBBR) infrastructure to companion bank blood and urine samples points alongside the trial. Network sites will not be participating in this companion study.

At the time of trial consent, at the discretion of the treating physician and PI, patients may be asked to simultaneously enroll in the DBBR as a companion banking study (RPCI protocol I 03103). Study team members will register the banking consent and associated enrollment information with DBBR, provide patients with the baseline DBBR epidemiologic questionnaire, and schedule blood and urine sample collection using the DBBR shared resource laboratory calendar, following standard work instructions for companion banking.

The DBBR is a shared institutional core resource where participants are asked to donate blood for research (prior to and following treatments), to complete an epidemiologic questionnaire, and to give permission to have their blood specimens linked to the questionnaire and clinical data including diagnosis and laboratory test results for research. Collected biospecimens and/or data are provided to investigators with RPCI IRB approved research protocols.

Patients that have already donated and banked appropriate pre-treatment specimens through another RPCI service and are usable for this study, will not be asked to donate additional pre-treatment (baseline) specimens. All samples and associated sample data from DBBR will be linked to the clinical data collected by the trial Coordinators, and de-identified prior to receipt for analysis. Per protocol, the DBBR will maintain the key between

the participant's PHI and study ID. Only designated DBBR personnel associated with operating the bank have access to this link. The key will never be given to the investigator of this study.

Participation in sample collection with the DBBR is optional.

1.2.1 Future Potential Studies

A variety of blood and urine markers have been found to be associated with outcomes and treatment effects. At the time of completion of this study, we will identify the most promising of these markers and retrospectively review some of the samples banked at the DBBR. Patients will be consented for this possibility.

1.2.2 FDG-PET staging and follow-up

The value of FDG-PET in NSCLC staging has been established and is accepted[35]. FDG-PET for staging is even accepted by the NCCN guidelines. Recent publications suggest that FDG-PET can be a predictor of response following conventional radiation therapy[36] and SBRT[37, 38]. Though fewer than fifty patients were involved in these studies, in practice FDG-PET is widely used and reimbursed for follow-up.

1.2.3 Pulmonary Function Testing

Paludan et al. analyzed the association of dose-volume histogram parameters with changes in dyspnea. Of 28 medically inoperable stage I NSCLC patients that received SBRT to 45 Gy/3 fractions over 5-8 days, aggravated dyspnea was registered in 11 patients (40%). Disturbingly, no association between DVH parameters and changes in dyspnea was found. Upon further analysis, the authors found observed that aggravation of dyspnea following SBRT reflected underlying COPD rather than treatment-related toxicity. The authors concluded that concern about pulmonary toxicity should not be prohibitive for future studies targeting limitations to dose and volume[39].

This experience highlights the need for close follow-up of pulmonary function following radiation therapy.

1.3 Roswell Park Cancer Institute Experience to Date

Since March 2006 we have treated 23 NSCLC patients with SBRT (60 Gy in 3 fractions.) No significant toxicities have been seen.

In addition, Cleveland Clinic is a high volume center for SBRT. They have expressed an interest in joining this study. The administrative process is underway. For this reason the stratification variables were changed to performance status and treatment center.

2.0 STUDY PURPOSES AND OBJECTIVES

2.1 Primary:

2.1.1 To compare incidence of toxicity with two established SBRT regimens for NSCLC

2.2 Secondary:

2.2.1 To compare QOL, patterns of failure, disease free survival, and overall survival associated with 2 two established SBRT regimens for NSCLC
2.2.2 To correlate outcomes and toxicities with imaging and patient and tumor biomarkers

3.0 ELIGIBILITY CRITERIA

3.1 Inclusion criteria

- Histologically confirmed NSCLC
- T1-T2, N0 measuring ≤ 5 cm (T3 based on chest wall involvement is excluded)
- Surgically resectable primary, however patient evaluated by thoracic oncologist and deemed medically inoperable **or** patient refuses surgical resection
- Age ≥ 18

3.2 Exclusion Criteria

- Prior Thoracic Radiation Therapy
- T2 or T3 tumor greater than 5 cm or T3 tumor based on chest wall involvement
- Node positive or metastatic disease
- Tumor location within the zone of the proximal bronchial tree. The proximal bronchial tree is defined as the carina, right and left main bronchi, right and left upper lobe bronchi, bronchus intermedius, right middle lobe bronchus, lingular bronchus, and right and left lower lobe bronchi. The *zone* of the proximal bronchial tree is defined as a volume 2cm in all directions around the proximal bronchial tree.
- Other conditions deemed by the PI or associates to make the patient ineligible for protocol investigations, procedures, and high-dose external beam radiotherapy. This includes the inability to cooperate with any aspect of SBRT such as the inability to lie still and breathe reproducibly.
- Pregnant or unwilling to use adequate contraception.

4.0 PRE-TREATMENT EVALUATION

4.1 Clinical Evaluation

- Evaluation by thoracic surgical oncologist
- Evaluation by radiation oncologist
- Performance status

4.2 Pre-treatment Data Acquisition

- PFT's (Full spirometry and DLCO)
- Urine pregnancy test for women of child bearing potential
- PET-CT
- CT of the Chest/Abdomen/Pelvis (CT Simulation is acceptable. The abdomen and pelvis CT studies may be omitted if the PET-CT covers the abdomen and pelvis.)
- Tumor Biopsy
- Specimens for banking: blood and urine (will be requested but is optional)
- Toxicity evaluation
- Quality of Life Questionnaire

5.0 INFORMED CONSENT

An informed consent for this trial meeting Federal and Institutional requirements will be obtained from each patient prior to enrollment in the study. The informed consent will inform each patient of what is involved, the risks, alternatives, who to contact for questions and that participation is voluntary. Additionally, patients will be asked to consent to the RPCI Data Bank and BioRepository as a companion study for future analyses (I 03103). Participation in this DBBR companion study, though encouraged, is at the discretion of the treating physician and PI. Participation in the DBBR is not required for participation in this trial. Patients who have already consented to the DBBR companion study will not need to be re-consented or have their pre-treatment samples re-drawn if done previously. Network sites will not be participating in this DBBR companion study.

6.0 TREATMENT PLAN

6.1 Study Design

Medically inoperable patients with node negative, peripherally located, biopsy proven NSCLC measuring ≤5 cm will be enrolled, stratified, and randomized to receive multi-fraction or single fraction SBRT.

Patients will be stratified by KPS into one of three groups (See Appendix IV) and treatment center. (100, 90, 80 and below).

Prior to SBRT delivery, patients will undergo baseline imaging using PET/CT and will undergo formal pulmonary function testing. Blood and

urine samples will also be formally collected and stored for future correlative studies.

Patients randomized to the multi-fraction arm will receive 3 high dose fractions of radiation to the primary lung tumor. Those randomized to the single fraction arm will receive a single high dose fraction using SBRT. Overall treatment time for one fraction is one day, for three fractions is 8-24 days. Treatment may start within 4 weeks after registration.

SBRT is a technique that allows for improved precision of radiation delivery. In order to deliver stereotactic radiotherapy, precise mechanisms of patient immobilization, tumor localization, and beam delivery are required and discussed in detail below.

Following SBRT delivery, imaging and pulmonary function studies will be regularly performed to monitor tumor status and toxicity. Blood and urine, samples may also be formally collected and stored, as described above, following SBRT and in the event of tumor recurrence such that correlative studies can be performed.

6.2 Protocol Administration

6.2.1 Dose Specifications

Note: Intensity Modulated RT (IMRT) Is Not Allowed without approval of PI.

6.2.1.1 *Stereotactic Targeting and Treatment*

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. This differs from conventional radiation therapy in which therapy is directed toward skin marks or bony landmarks that are indirectly referenced to the tumor. 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. The nature of the fiducials themselves may include radio-opaque markers or rods placed at known locations in a frame or fixed structure adjacent to the patient as well as use of the tumor itself as a fiducial (e.g. acquiring tomographic views of the tumor simultaneously with the treatment). Metallic “seeds” placed within the tumor will not

generally be allowed to constitute a fiducial unless the site employing this technique provides satisfactory validation to the Study Chair indicating no seed migration and reproducibility of target positioning from treatment to treatment and obtains permission in writing from the Study Committee (Principal Investigator and Co-Chairs) prior to treatment.

6.2.1.2 *Dose Fractionation*
Patients will receive 1 (30 Gy) or 3 (20 Gy) fractions of radiation. 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). The dose for all patients per fraction will be to the prescription line at the edge of the PTV. If giving 3 fractions, treatment will be delivered as above over 8-24 days for a total of 60 Gy. Overall treatment time for one fraction is one day, for three fractions is 8-24 days. Treatment may start within 4 weeks after registration.

6.2.1.3 *Premedications*
Unless contraindicated, it is recommended that all patients receive corticosteroid premedication (e.g. Decadron 4 mg p.o. in a single dose, or equivalent) 15-60 minutes prior to each of the treatment 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.

6.2.2 Technical Factors

6.2.2.1 *Physical Factors*
Only photon (x-ray) beams produced by linear accelerators, betatrons, or microtron accelerators with photon energies 6-23 MV will be allowed. Cobalt-60 and charged particle beams (including electrons, protons, and heavier ions) are not allowed. Photon beam energies greater than 6 MV but not more than 23 MV will only be allowed for a limited number (≤ 2) beams that must travel more than a cumulative distance of 10 cm through soft tissue (not lung) to reach the isocenter.

6.2.2.2 *Minimum Field Aperture (Field Size) Dimension*
Due to uncertainties in beam commissioning resulting from electronic disequilibrium within small beam apertures, a minimum field dimension of 3.5 cm is required for any field used for treatment delivery. It is understood that this may exceed the technical requirements listed in Section 6.4 for small lesions (< 2.5 cm axial GTV dimension or < 1.5 cm cranio-caudal GTV dimension). In such cases, the prescription dose is still prescribed to the edge of the defined PTV. This minimum field dimension does not apply to centers using tomotherapy or multiple pencil beam delivery systems.

6.2.2.3 *Dose Verification at Treatment*
Personal dosimeter measurements (e.g. diode, TLD, etc.) may be obtained for surface dose verification for accessible beams as per institutional preference. This information is not required by the protocol.

6.2.3 Localization, Simulation, and Immobilization

6.2.3.1 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.

It is very important that a rigid immobilization device be prepared in the CT Simulator to ensure reproducible set up of the patient during his/her treatment. Selection of an appropriate immobilization device will be done after consulting with the physician who may elect to use one or many such immobilization devices together [e.g. BodyFix along with vaclock system etc.] for a particular patient.

6.2.3.2 Internal Organ Motion/ Tumor Localization
Patients will undergo simulation using a respiratory gating technique which synchronizes radiation delivery to an individual's breathing cycle. Image acquisition takes place only during a pre-specified portion of the respiratory cycle (maximum inhalation or end-expiration) thus helping to determine margins needed to encompass tumor motion throughout the breathing cycle. Respiratory gating will be used only for determination of ITV and is not used for actual treatment delivery.

Due to significant intrafraction motion of the tumor, it is proposed to use respiratory gating to determine the maximum extent of tumor motion by taking at least 2 additional scan sets/series viz. exhale and inhale phase. The gated CT image set can cover a much smaller superior-inferior extent. These limits will be defined by the radiation oncologist and are usually 2 cm beyond the GTV limits defined earlier utilizing the topogram/scout view. The patient is now instructed to breathe in a reproducible manner. Using the RPM system, appropriate threshold levels are then generated for phase based gating enabling gated CT-data acquisition in the inhale and exhale stage**. It is very important to ensure that the couch parameters and the patient position remain unchanged in all the three series acquisitions [normal breathing, exhale & inhale state].** The necessary gating parameters, as well as the other series identification information will be recorded in the conventional free-breathing gating sheet in use for such patients and will be attached with the patient's chart. It is important to remember that the

above procedure mentioned for determining the ITV is strictly true only for the single-slice CT scanner allowing prospective gating scans.

In some lung SBRT cases, it may not be possible to use RPM gating system to acquire the additional scans in inhale and exhale phase as the patient may be having very shallow breathing pattern. In those type of circumstances, it might be easier to acquire a cone beam CT scan (CBCT). The CBCT will then be co-registered with regular normal breathing CT simulation image series and will be used instead of the inhale and exhale image series obtained through respiratory gating. Cone beam CT images will be taken just prior to delivery of each radiation fraction while the patient is in the treatment position on the linear accelerator. These CT images can be compared with the original treatment planning CT and adjustments can be made as necessary to precisely conform treatment delivery to the original plan. This process may be repeated during RT more than once per physician discretion.

Cone beam CT will give an idea about the average tumor motion as the CBCT image is reconstructed using 550+ planar images acquired in around 1 minute. Such an image can either be acquired directly using CBCT application or can also be generated through the regular process of 3D/3D match. Please note that prior to acquiring these CBCT images, the patient will be repositioned on the Trilogy couch exactly the same way as it was on the CT Simulator. The reconstructed CT images can then be imported and registered in Eclipse. Since OBI station is on its own network, a direct transfer of the patient files which are in D:\patient\MR# directory is not possible but Compact disks [CDR] can be used to burn the images. Virus free flash drives may also be used for this purpose.

Tumor localization methods are constantly evolving. As other accepted methods of tumor localization become available, including image based and implantable fiducial marker based methods, these may be substituted at the PI's discretion.

6.2.4 Treatment Planning/Target Volumes

6.2.4.1 Image Acquisition

Computed Tomography (CT) 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. If IV contrast dye is used, then 1) 2 sets of images one without the dye and one with the dye should be done or 2) a bulk density must be defined in the treatment planning system for the region of dye. Axial acquisitions with gantry 0 degrees will be required

with spacing ≤ 3.0 mm between scans. Images will be digitally transferred to the treatment planning computers.

Once images have been transferred to the planning system, the target lesion and surrounding normal tissue structures will be outlined by the treating physician. 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. The Gross Tumor Volume (GTV) is defined as the visible tumor on CT. No margin will be added for presumed microscopic extension. The Clinical Target Volume (CTV) and GTV are thus identical.

There are 2 acceptable methods to define the PTV depending on the method of CT simulation:

(a) Conventional (helical) CT-simulation (non-4DCT): The PTV will include the GTV plus an additional 0.5 cm margin in the axial plane and 1.0 cm margin in the longitudinal plane (craniocaudal).

(b) 4D CT-simulation: An internal target volume (ITV) around the GTV, accounting for tumor motion may be defined from the 4D CT dataset. The PTV will include the ITV plus an additional 0.5 cm margin uniformly applied to the ITV.

These margins will be used at all institutions, even if a particular institution uses equipment or techniques felt to be more accurate.

6.2.4.2 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, 7-10 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 7 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, the isocenter is defined as the common point of gantry, collimator, and couch rotation for the treatment unit. 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 build up at the edges of the blocks or MLC jaws beyond the PTV). The only exception will be when observing the minimum field dimension of 3.5 cm when treating small lesions. As such, prescription lines covering the PTV will

typically be the 60-90% line (rather than 95-100%); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. The isocenter in stereotactic coordinates 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. The plan should be normalized to a defined point corresponding closely to the center of mass of the PTV (COM_{PTV}). Typically, this point will be the isocenter of the beam rotation; however, it is not a protocol requirement for this point to be the isocenter. Regardless, the point identified as COM_{PTV} must have defined stereotactic coordinates and receive 100% of the normalized dose. Because the beam apertures 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%. The prescription dose of 60 Gy in three fractions will be delivered to the margin of the PTV and fulfill the requirements below. As such, a "hot spot" will exist within the PTV centrally at the COM_{PTV} with a magnitude of 60 Gy times the reciprocal of the chosen prescription isodose line (i.e., 60-90%).

Tissue heterogeneity corrections **will not be used for the patient's treatment.** For purposes of dose planning and calculation of monitor units for actual treatment, all tissues within the body, including lung, will be assumed to have unit (water) density (no correction for tissue heterogeneity).

Once a treatment plan has been approved, an additional treatment plan will be generated with inhomogeneity correction ON. However, this plan will be altered in such a way that it carries the monitor units of the inhomogeneity OFF treatment plan. The dose to various critical structures and dosimetric indices will be recorded for documentation purposes in another worksheet which will have all the parameters as specified earlier as well as following parameters [volume of PTV receiving 60 Gy {or 30 Gy in case of single dose SBRT} or more [V_{60}] and D_{95}]. The exact inhomogeneity correction algorithm to be used for these patients will be the same which is being used for rest of the patients being treated at RPCI. Of note, the calculation grid utilized should be as small as possible.

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.

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 (i.e., 20 Gy per fraction = 60 Gy total; 30 Gy single fraction = 30 Gy total)), and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose (i.e., 18 Gy per fraction = 54 Gy total for 3 fraction regimen; 27 Gy for single fraction regimen).

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 1) above.

4) High Dose Spillage

a) Location

Any dose greater than 105% of the prescription dose (> 21Gy per fraction = 63 Gy total for 3 fraction regimen; >31.5 Gy for single fraction) should occur primarily within the PTV itself and not within the normal tissues outside of the PTV. Therefore, the cumulative volume of all tissue outside of the PTV receiving a dose greater than 105% of prescription dose (> 21Gy per fraction = 63 Gy total for 3 fraction regimen; >31.5 Gy for single fraction) should be no more than 15% 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 (< 2.5 cm axial GTV dimension or < 1.5 cm cranio-caudal GTV dimension) where the required

minimum field size of 3.5 cm results in the inability to meet a conformality ratio of 1.2.

5) Low 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 be no greater than D_{2cm} where D_{2cm} is given by the table below.

b) Volume

The ratio of the volume of 50% of the prescription dose (10 Gy per fraction = 30 Gy total for 3 fraction regimen; 15 Gy for single fraction) isodose to the volume of the PTV must be no greater than $R_{50\%}$ where $R_{50\%}$ is given by the table below.

TABLE 1: Conformality Criteria and Lung Radiation Limits

Maximum PTV Dimension (cm)	Ratio of Prescription Isodose Volume to PTV		Ratio of 50% Prescription Isodose Volume to PTV ($R_{50\%}$)		Maximum Dose 2cm from PTV in any Direction (in Gy)		Percent of Lung receiving 20 Gy total or more V20 (%)		PTV volume (in cc)
	Deviation		Deviation		Deviation		Deviation		
	None	Minor	None	Minor	None	Minor	None	Minor	
2.0	<1.2	1.2 – 1.4	< 3.9	3.9 – 4.1	< 28.1	28.1 – 30.1	< 10	10 - 15	1.8
2.5	<1.2	1.2 – 1.4	< 3.9	3.9 – 4.1	< 28.1	28.1 – 30.1	< 10	10 – 15	3.8
3.0	<1.2	1.2 – 1.4	< 3.9	3.9 – 4.1	< 28.1	28.1 – 30.1	< 10	10 - 15	7.4
3.5	<1.2	1.2 – 1.4	< 3.9	3.9 – 4.1	< 28.1	28.1 – 30.1	< 10	10 – 15	13.2
4.0	<1.2	1.2 – 1.4	< 3.8	3.8 – 4.0	< 30.4	30.4 - 32.4	< 10	10 – 15	21.9
4.5	<1.2	1.2 – 1.4	< 3.7	3.7 – 3.9	< 32.7	32.7 – 34.7	< 10	10 – 15	33.8
5.0	<1.2	1.2 – 1.4	< 3.6	3.6 – 3.8	< 35.1	35.1 – 37.1	< 10	10 – 15	49.6
5.5	<1.2	1.2 – 1.4	< 3.5	3.5 – 3.7	< 37.4	37.4 – 39.4	< 10	10 – 15	69.9
6.0	<1.2	1.2 – 1.4	< 3.3	3.3 – 3.5	< 39.7	39.7 – 41.7	< 10	10 – 15	95.1
6.5	<1.2	1.2 – 1.4	< 3.1	3.1 – 3.3	< 42.0	42.0 – 44.0	< 10	10 – 15	125.8
7.0	<1.2	1.2 – 1.4	< 2.9	2.9 – 3.1	< 44.3	44.3 – 46.3	< 10	10 – 15	162.6

7.5	<1.2	1.2 – 1.4	< 2.7	2.7 – 2.9	< 46.6	46.6 – 48.6	< 10	10 – 15	
8.0	<1.2	1.2 – 1.4	< 2.5	2.5 – 2.7	< 48.9	48.9 – 50.9	< 10	10 – 15	

Note 1: For values of PTV dimension or volume not specified, linear interpolation between table entries is required.
Note 2: Protocol deviations greater than listed here as 'minor' will require approval of the treating physician or PI prior to treatment.
Note 3: These limits will apply to both treatment arms.

6) Respect all critical organ dose-volume limits listed in Section 6.5.1 below.

6.2.5 Critical Structures

6.2.5.1 Critical Organ Dose-Volume Limits

The following table lists maximum dose limits to a point or volume within several critical organs. These are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation.
The limits for 20Gy x 3 are taken from RTOG 0236 and were formulated with the approval of the RTOG study committee (Principal Investigators and Co-Chairs) including Dr. Jack Fowler, international authority on radiobiology and radiotolerance, using known tolerance data, radiobiological conversion models, norms used in current practice at academic centers,[16-22] and the experience of several years of irradiation using these large fractions at Indiana University[26,30,31] and centers in Sweden,[24,25,27] Germany, and Japan. With the exception of the spinal cord limit which is conservatively set from experience with irradiation of vertebral body metastases, the dose limits for 30 Gy were scaled from the limits at 20 Gy per fraction. However, even for the 30 Gy arm, **we will endeavor to meet the single fraction dose limits** of the 20 Gy arm.

In order to verify each of these limits, the organs must be contoured such that appropriate dose volume histograms can be generated. Instruction for the contouring of these organs will follow below.

TABLE 2a: DOSE LIMITS TO CRITICAL STRUCTURES for 20 Gy x3

Organ	Volume	20 Gy x 3 Arm
Spinal Cord	Any point	18 Gy (6 Gy per fraction)
Esophagus	Any point	27 Gy (9 Gy per fraction)
Ipsilateral Brachial Plexus	Any point	24 Gy (8 Gy per fraction)
Heart	Any point	30 Gy (10 Gy per fraction)
Trachea and Ipsilateral Bronchus	Any point	30 Gy (10 Gy per fraction)
Whole Lung (Right & Left)	(See table in Section 6.4.2)	(See table below)

TABLE 2b: DOSE LIMITS TO CRITICAL STRUCTURES for 30 Gy x1

Serial Tissue	**Volume**	**Volume Max (Gy)**	**Max Point Dose (Gy)**	**Endpoint (≥Grade 3)**
Spinal Cord	<0.35 cc <1.2 cc	10 Gy 7 Gy	14 Gy	myelitis
Esophagus*	<5 cc	11.9 Gy	15.4 Gy	stenosis/fistula
Brachial Plexus	<3 cc	14 Gy	17.5 Gy	neuropathy
Heart/Pericardium	<15 cc	16 Gy	22 Gy	pericarditis
Great vessels	<10 cc	31 Gy	37 Gy	aneurysm
Trachea and Large Bronchus*	<4 cc	10.5 Gy	20.2 Gy	stenosis/fistula
Rib	<1 cc	22 Gy	30 Gy	Pain or fracture
Skin	<10 cc	23 Gy	26 Gy	ulceration
Stomach	<10 cc	11.2 Gy	12.4 Gy	ulceration/fistula
Parallel Tissue	Critical Volume (cc)	**Critical Volume Dose Max (Gy)**		**Endpoint (≥Grade 3)**
Lung (Right & Left)	1500 cc	7 Gy		Basic Lung Function
Lung (Right & Left)	1000 cc	7.4 Gy		Pneumonitis

6.2.5.2 Contouring of Normal Tissue Structures

6.2.5.2.1 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.

6.2.5.2.2 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.

6.2.5.2.3 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 using the subclavian and axillary vessels as a surrogate for identifying the location of the brachial plexus. This neurovascular complex 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 2nd rib.

6.2.5.2.4 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.

6.2.5.2.5 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 (see section 6.5.2.8 below).

6.2.5.2.5.1 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 (which ever is more superior) and continue inferiorly to the superior aspect of the proximal bronchial tree (see definitions below).

6.2.5.2.5.2 Proximal Bronchial Tree

The proximal bronchial tree will include the most inferior 2 cm of distal trachea and the proximal airways. The following airways will be included according to standard anatomical 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.

6.2.5.2.6 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.

6.2.5.2.7 PTV Plus 2 cm

As part of the QA requirements for “low dose spillage” listed in 6.2.4.2 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.

6.2.5.2.8 Proximal Bronchial Tree Plus 2 cm

As part of adhering to the ineligibility requirements for not enrolling patients with tumors in the zone of the proximal bronchial tree, 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. Most treatment

planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning. This structure is not required by the protocol, but its construction is suggested to facilitate appropriateness of patient selection. Alternately, ruler tools in the treatment planning software may be used to ensure protocol compliance.

6.2.6 Documentation Requirements

In general, treatment interruptions should be avoided by preventative medical measures and nutritional, psychological, and emotional counseling. Treatment breaks, including indications, must be clearly documented on the treatment record and communicated to the PI. The total treatment time following the first fraction, must not exceed 10 weeks.

6.2.6.1 Quality of Life Measures

Health related quality of life (HRQOL) will be assessed by study team members using 2 frequently used and validated questionnaires. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC-QLQ] C30) is a generic HRQOL questionnaire. A lung cancer-specific questionnaire (EORTC QLQ-LC13) will also be used[40-42]. Patient responses to these questionnaires will be used to analyze and quantify differences, if any, in HRQOL from each SBRT regimen. See Appendix II.

6.2.7 Compliance Criteria

6.2.7.1 Dosimetry Compliance

Section 6 describes appropriate conduct for treatment planning dosimetry. Criteria for both major and minor deviations are provided in the table in Section 6.2.4. In addition to the criteria in section 6.2.4, the table in Section 6.2.5 lists dose volume limits for specific organs and structures. Exceeding these limits by more than 2.5% constitutes a minor protocol violation. Exceeding these limits by more than 5% constitutes a major protocol violation.

6.2.7.2 Treatment Delivery Compliance

Set-up films will be compared to digitally reconstructed radiographs from the same beam's eye view. Deviations of less than 0.5 cm in the transverse plane and 1.0 cm in the cranio-caudal plane will be considered compliant. Deviations from 0.5-1.0 cm in the transverse plane and 1.0-1.25 cm in the craniocaudal plane will be considered minor protocol deviations.

Deviations greater than those listed as minor will be considered major protocol deviations.

6.2.8 Radiation Toxicity

The most commonly reported side effects from lung SBRT have been pulmonary side effects, likely attributable to radiation induced inflammation (radiation pneumonitis) of surrounding normal lung. The constellation of symptoms associated with radiation pneumonitis includes fatigue, fever, shortness of breath, nonproductive cough, and pulmonary infiltrates on chest x-ray.

Among 37 patients evaluated in a Phase I dose escalation study performed by Timmerman et al., all patients reported fatigue. Six patients reported worsening shortness of breath and non-productive cough and were treated with steroids, inhalers cough medicines, and oxygen therapy. On imaging studies, one patient was noted to have worsening pulmonary infiltration and 25 patients had worsening fibrotic changes. Following SBRT, 10 patients had documented decline of at least 10% predicted in at least one measure of pulmonary function. Other reported toxicities in this Phase I trial included chest wall tenderness and discomfort from the abdominal compression device and one report of grade 3 radiation dermatitis.

An update of this Phase I trial evaluating 47 patients, Grade 2 toxicities reported included pneumonitis, pericardial effusion, pneumonia, and bronchitis. Grade 3 toxicities reported included pneumonitis, hypoxia, dermatitis, pericardial effusion, pneumonitis, and tracheal necrosis.

Timmerman et al later reported the results of a Phase II trial that included 70 patients with a median follow-up of 17.5 months. 58 of 70 patients experienced grade 1-2 toxicity, most commonly fatigue, musculoskeletal discomfort, and radiation pneumonitis. Eight grade 3-4 toxicities were reported including decline in PFT's, pneumonia, pleural effusion, apnea, and skin reaction. Six grade 5 toxicities (deaths) were reported, 4 secondary to bacterial pneumonia, 1 from pericardial effusion, and 1 from massive hemoptysis following local recurrence adjacent to the carina. Further analysis of patients experiencing high grade toxicity revealed that tumor location was a significant predictor. Patients treated for tumors in the peripheral lung had 2-year freedom from severe toxicity of 83% compared with only 54% for patients with central tumors[30].

In a retrospective analysis of 138 patients reported by Baumann et al., 60% of patients reported no toxicity. Fourteen patients experienced grade 3-4 toxicity including lung atelectasis, rib fracture, pneumonitis, thoracic pain, pneumonia, decreased lung function, and decreased performance

status. The most commonly reported toxicities included lung fibrosis (n=21), skin rash (n=12), lung atelectasis (n=10), cough (n=9), rib fracture (n=8), thoracic pain (n=6), esophagitis (n=5), and pleural exudates (n=4).

Hara et al reported toxicity outcomes among 59 patients treated for malignant lung tumors with single fraction SBRT ranging from 20-34 Gy. In one patient, grade 2 respiratory symptoms were reported and in one patient with active tuberculosis and interstitial pneumonia, Grade 3 respiratory toxicity requiring oxygen supplementation was reported. Two patients experienced skin erythema.

In another trial of single fraction SBRT, Hof et al reported outcomes among 42 patients treated with a single fraction ranging from 19-30 Gy. Follow up CT scan normal tissue changes (including pneumonitic changes and fibrosis) were noted in the treatment area in 64.3% of patients. However, no CTC grade 3 or 4 toxicities were noted. Minor cough and slightly increased dyspnea were the only clinical toxicities observed.

The Japanese experience was reported retrospectively by Onishi et al. Among 257 patients treated with various dosing schemes (1-22 fractions at 3-12 Gy per fraction). NCI-CTC pulmonary toxicities ≥ grade 2 were reported in 10.9% of patients. Grade 3 or 4 toxicities were observed in 5.4% and included bronchitis, esophagitis, dermatitis, and rib fracture. The vast majority of patients experiencing symptomatic pulmonary complications had baseline pulmonary fibrosis or emphysema.

7.0 STUDY CALENDAR

	Pre-Treatment[11]	Rx #1[10]	Rx #2	Rx #3[9]	6 wks post-rx	12 wks post-rx	f/u[1,11]
H&P[8]	X	X	X	X	X	X	X
Performance Status	X	X	X	X	X	X	X
Evaluation by Thoracic Oncologist	X						
Evaluation by Radiation Oncologist	X						
Pregnancy test	X						
CT C/A/P[7]	X						
PET-CT scan[7]	X						X[2]
PFT's[6]	X						X[3]
Tumor Biopsy	X						X[4]
Blood and urine, collection for DBBR, future analyses[5]	X						
Toxicity Eval	X	X	X	X	X	X	X
QOL questionnaire	X	X	X	X	X	X	X

[1] At week 6 and 12 post SBRT as noted above, then every 3 months for 1 year, and every 6 months for the next 4 years. Patients will be followed for a total of 5 years.
[2] PET-CT will be done at 6 months and then as clinically indicated
[3] PFTs will be done at 6 months, and annually in follow-up
[4] Biopsies will be done only if clinically indicated.
[5] Blood and urine will be collected through the DBBR at pre-treatment. Patients may refuse this and still participate in the study. This will not be offered at network sites.
[6] Full Spirometry and DLCO
[7] Any one of these pre-treatment imaging studies should be done within 6 weeks of registration: CT Chest, PET or CT Simulation
[8] H&P within 2 weeks of treatment start
[9]Overall treatment time for one fraction is one day, for three fractions is 8-24 days.
[10]Treatment may start within 4 weeks after registration.
[11]Pre-treament and follow up assessments may be waived at the discretion of the Principal Investigator.

8.0 TREATMENT MODIFICATIONS

8.1 Radiation Treatment Modifications

Modifications to the radiation treatment will be discussed with the Principal Investigator.

8.2 Off Study Criteria

8.2.1 Patients may be taken off study for the following non-medical or administrative reasons:

- Patient refuses the procedure or further treatment
- It is deemed in the patient's best interest as determined by the PI.
- Serious protocol violation as determined by the PI.

8.2.2 Development of a concurrent serious medical condition that precludes the completion of fiducial marker placement, radiation therapy or follow-up.

8.2.3 Tumor progression (if occurs during treatment, at the end of radiation therapy unless the completion of local therapy is not indicated)

8.2.4 Initiation of cytotoxic chemotherapy (if occurs during treatment, at the end of radiation therapy unless the completion of local therapy is not indicated)

8.2.5 Development of a concurrent serious medical condition during active treatment and not attributable to therapy that precludes the completion of active treatment.

8.2.6 The completion of 60 months (5 years) follow-up.

9.0 RESPONSE CRITERIA

This protocol will use a modified version of the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3): 205-216, 2000] See http://ctep.info.nih.gov/guidelines/recist.html for further details. Additional definitions beyond the RECIST guidelines specific to this protocol are incorporated to define local control as described below.

9.1 Baseline documentation of "Target" and "Non-Target" Lesions

Patients enrolled to this protocol should have clinical stage I (T1 or T2, N0, M0) or clinical stage II (non-small cell lung cancer. At time of treatment, they should only have one site of gross disease in the lung with no metastases. The primary lung tumor should be identified as the ***target lesion*** and recorded and measured at baseline and with each follow-up imaging evaluation.

The longest diameter (LD) for *the target lesion* will be calculated **from the treatment planning CT scan** using pulmonary windowing and reported as the baseline LD. The baseline LD will be used as reference by which to characterize the objective tumor. For follow-up assessment, diagnostic CT scans performed using a 5 mm contiguous reconstruction algorithm using pulmonary windowing taken as part of scheduled protocol follow-up are preferred as the method of evaluation for response. When CT scans are not available, chest x-ray determination will be allowed as long as the target lesion is clearly visible. Changes in serum tumor markers will not be allowed for assessment of either local tumor progression or metastatic progression.

Local treatment effects in the vicinity of the tumor target may make determination of tumor dimensions difficult. For example, bronchial or bronchiolar damage may cause patchy consolidation around the tumor that over time may coalesce with the residual tumor. In cases where it is indeterminate whether consolidation represents residual tumor or treatment effect, it should be assumed that abnormalities are residual tumor. A treating radiation oncologist will review films as well as a radiologist at each site.

All other lesions (or sites of disease) that appear after treatment (e.g., regional lymph nodes and distant metastases) should be identified as ***non-target lesions*** and should also be recorded at the point of their appearance and with each follow up. Non-target lesions should constitute measurable disease, which by definition requires having an appearance suspicious for carcinoma and having a dimension of at least 1.0 cm. Assessment of regional lymphatic or metastatic progression will be made in comparison to the required pretreatment staging studies or any other pretreatment imaging evaluations available. Only non-target lesions appearing at the margin of the PTV (i.e., within 1.0 cm) will have recorded measurements (see Marginal Failure in the table below). Recorded measurements of all other non-target lesions are not required, but the presence or absence of each should be noted throughout follow-up.

9.2 Response Criteria

Evaluation of Target Lesions	
Complete Response **(CR)**	Disappearance of the target lesion; ideally, this determination will be made based on CT image evaluation.
Partial Response **(PR)**	At least a 30% decrease in the LD of the target lesion, taking as reference the baseline LD; ideally, this determination will be made based on CT image evaluation.
Stable Disease **(SD)**	Neither sufficient shrinkage to qualify for CR/PR above nor sufficient increase to qualify for LE below, taking as reference the smallest LD since the treatment started
Local Enlargement **(LE)**	At least a 20% increase in the LD of target lesion, taking as reference the smallest LD recorded since the treatment started; Ideally, this determination will be made based on CT image evaluation.
Local Failure **(LF)**	Refers to the primary treated tumor after protocol therapy and corresponds to meeting both of the following two criteria: 1) Increase in tumor dimension of 20% as defined above for local enlargement (LE); 2) The measurable tumor with criteria meeting LE should be avid on Positron Emission Tomography (PET) imaging with uptake of a similar intensity as the pretreatment staging PET, OR the measurable tumor should be biopsied confirming viable carcinoma. For outcome analysis, Marginal Failures (MF; see below) will also be counted as LF; however, they should be distinguished specifically as MF, not LF, on all report forms. The EORTC criteria for post-treatment PET evaluation will be used as a basis for evaluation in cases more difficult to assign as to whether the uptake is pathological for cancer recurrence vs. inflammation.[46]
Local Control **(LC)**	The absence of Local Failure.
Progressive Disease (PD)	Progression will be defined by any

	imaging and clinical findings which support development of disease outside the chest, in the mediastinum or first echelon lymph nodes, and by PET +/- biopsy consistent with progression at the target lesion.

10.0 ADVERSE EVENTS

Network sites refer to Appendix III for AE and SAE reporting instructions.

10.1 Adverse Events Reporting

Investigators are required by Federal Regulations to report serious adverse events to the Study Chair and Clinical Research Services. CRS will notify the Institutional Review Board if a patient has a reportable serious adverse event. This study will utilize the Common Toxicity Criteria version 3.0 to determine the severity of the reaction for adverse event reporting. (Appendix I)

Reporting requirements and procedures depend upon: (1) whether procedure is suspected of causing the adverse event, (2) whether the possibility of such an adverse event was reported in the protocol, consent form, or manufacturer's literature (expected or unexpected adverse event), (3) the severity or grade of the adverse event, (4) the phase of the study and attribution (the determination of whether an adverse event is related to a medical treatment or procedure). All reactions in a "reportable" category must be reported.

10.2 Serious Adverse Events (SAE)

- A serious adverse event (SAE) is any experience that suggests a significant hazard, contraindication, side effects or precaution. This includes any experience that:
- Results in death.
- Is a life-threatening adverse drug experience.
- Requires inpatient hospitalization or prolongation of existing hospitalization.

  For the purpose of this study, hospitalizations for protocol-scheduled procedures, blood product transfusions, or for social reasons (i.e., awaiting transport home) will not be considered SAE's.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Requires medical or surgical intervention to prevent one of the outcomes listed above.

10.3 Reporting Serious Adverse Events

All serious adverse events will be reported to the IRB and Data Safety Monitoring Board according to the established guidelines. A cumulative summary of all adverse events occurring on this study will also be submitted to the IRB with the continuing review. Toxicity is reported, as required, to the FDA and study sponsors. All study data reviewed and discussed during these meetings will be kept confidential. Any breech in subject confidentiality will be reported to the IRB. In addition, all Roswell Park Cancer Institute initiated trials will be monitored periodically by the Compliance Monitor.

10.4 SAE Follow-up

For all SAE's occurring during the study or within 30 days of the last administration of study procedure, the investigator must submit follow-up reports the Study Chair and Clinical Research Services, CRS will notify Institutional Review Board regarding the patient's subsequent course until the SAE has subsided, or until the condition stabilizes, the patient dies, or receives alternative therapy.

Local reporting for data and safety monitoring for the protocol will require SAE's to be reported to the IRB, via the Clinical Research Service Office, using the Adverse Event Reporting form and the FDA MEDWATCH SAE reporting form.

On the anniversary date of the approved protocol at RPCI, the principal investigator will be required to report to the IRB the number of patients entered on the trial, the number of patients treated, a summary of all adverse events reported to date using CTC 3.0 grading, a specific list of serious adverse events requiring immediate reporting, and significant literature reporting developments that may affect the safety of participants or the ethics of the study.

11.0 DATA SAFETY AND MONITORING PLAN

- PI will assume primary responsibility for monitoring the progress of the trial and the safety of participants.
- Data will be submitted to the RPCI IRB annually for continuing review and at the completion of the study.
- Data integrity and protocol adherence are assured by regular data verification and protocol compliance checks performed by the research team (PI, research nurse, data manager and clinic nurse).

The IRB will review annual data and safety monitoring reports, as well as an interim analysis performed after 49 patients have been enrolled, and make recommendations on whether the study should continue unchanged, require

modification/amendment, or be closed based on unacceptable risk to participants.

12.0 STATISTICAL ANALYSIS

This is a phase II randomized study to compare incidence of RTOG grade 3 or higher toxicity associated with 2 different, established SBRT regimens for NSCLC.

Group sample sizes of 49 in group one (Gy x 3) and 49 in group two (Gy x 1) achieve 81% power to detect a difference between the group incidences of toxicity of 0.17. The incidence of toxicity in group one (the treatment group) is assumed to be 0.03 under the null hypothesis and 0.2000 under the alternative hypothesis. The proportion in group two (the control group) is 0.03. The test statistic used is the one-sided Z test with continuity correction and unpooled variance. The significance level of the test was targeted at 0.05. The significance level actually achieved by this design is 0.0037.

Descriptive statistics will be presented for each group. Incidence of toxicity will be compared using Z test. Disease free survival and overall survival will be compared between two groups using log-rank test statistics. Correlation analysis will be performed to explore the relationship between outcomes and toxicities with tumor biomarkers. The estimate of acute and long term toxicity associated with SBRT for NSCLC will be reported.

13.0 SAMPLE HANDLING

13.1 Blood and Urine Samples

Forty (40) ml of blood will be collected, processed, and stored in the RPCI Data Bank and BioRepository at the time points specified in the study calendar. The DBBR will distribute the de-identified samples to the study investigators using established DBBR procedures.

At least 20 and up to 100 ml of spot urine samples will also be collected and stored at -20 ^{o}C in the RPCI Data Bank and BioRepository at the time points specified in the study calendar. The DBBR will distribute the de-identified samples to the study investigators using established DBBR procedures.

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APPENDIX I

COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) VERSION 3.0

Pulmonary/Upper Respiratory

Adverse Event	Short Name	1	2	3	4	5
Adult Respiratory Distress Syndrome	ARDS	-	-	Present, intubation not indicated	Present, intubation indicated	Death
Aspiration	-	Asymptomatic ("silent aspiration"); endoscopy or radiographic (e.g., barium swallow) findings	Symptomatic (e.g., altered eating habits, coughing or choking episodes consistent with aspiration); medical intervention indicated(e.g., antibiotics, suction or oxygen)	Clinical or radiographic signs of pneumonia or pneumonitis; unable to treat aliment orally	Life-threatening (e.g., aspiration pneumonia or pneumonitis)	Death
Atelectasis	-	Asymptomatic	Symptomatic (e.g., dyspnea, cough), medical intervention indicated (e.g., bronchoscopic suctioning, chest physiotherapy, suctioning)	Operative (e.g., stent, laser) intervention indicated	Life-threatening respiratory compromise	Death
Bronchospasm, wheezing	-	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening	Death
Carbon monoxide diffusion capacity	DL_{CO}	90-75% of predicted value	<75-50% of predicted value	<50-25% of predicted value	<25% of predicted value	Death

Chylothorax	-	Asymptomatic	Symptomatic; thoracentesis or tube drainage indicated	Operative intervention	Life-threatening (e.g., hemodynamic instability or ventilatory support indicated)	Death
Cough	-	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or activities of daily living (ADL)	-	-

Adverse Event	Short Name	1	2	3	4	5
Dyspnea	-	Dyspnea on exertion, but can walk 1 flight of stairs without stopping	Dyspnea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1km) without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator indicated	Death
Edema, larynx	-	Asymptomatic edema by exam only	Symptomatic edema, no respiratory distress	Stridor; respiratory distress; interfering with ADL	Life-threatening airway compromise; tracheotomy, intubation, or laryngectomy indicated	Death
FEV_1	-	90-75% of predicted value	<75-50% of predicted value	<50-25% of predicted value	<25% of predicted value	Death
Fistula* - Bronchus - Larynx - Lung - Oral cavity - Pharynx - Pleura - Trachea	-	Asymptomatic, radiographic findings only	Symptomatic, tube thoracostomy or medical management indicated; associated with altered respiratory function but not	Symptomatic and associated with altered respiratory function interfering with ADL; or endoscopic (e.g., stent) or	Life-threatening consequences; operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death

			interfering with ADL	primary closure by operative intervention indicated		
Hiccoughs (hiccups, singultus)	-	Symptomatic, intervention not indicated	Symptomatic, intervention indicated	Symptomatic, significantly interfering with sleep or ADL	-	-
Hypoxia	-	-	Decreased O_2 saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased O_2 saturation at rest; continuous oxygen indicated	Life-threatening; intubation or ventilation indicated	Death
Nasal cavity/paranasal sinus reactions	-	Asymptomatic mucosal crusting, blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow	Stenosis with significant nasal obstruction; interfering with ADL	Necrosis of soft tissue or bone	Death

Adverse Event	Short Name	1	2	3	4	5
Obstruction/stenosis of airway - Bronchus - Larynx - Pharynx - Trachea	Airway obstruction	Asymptomatic obstruction or stenosis on exam, endoscopy, or radiograph	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Interfering with ADL; stridor or endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; tracheotomy or intubation indicated	Death
Pleural effusion (non-malignant)	-	Asymptomatic	Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated	Symptomatic and supplemental oxygen, >2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated	Life-threatening (e.g., causing hemodynamic instability or ventilatory support indicated)	Death
Pneumonitis/pulmonary infiltrates	-	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O_2 indicated	Life-threatening; ventilatory support indicated	Death
Pneumothorax	-	Asymptomatic, radiographic findings only	Symptomatic; intervention indicated (e.g., hospitalization for observation, tube placement without sclerosis)	Sclerosis and/or operative intervention indicated	Life-threatening, causing hemodynamic instability (e.g., tension pneumothorax); ventilatory support indicated	Death
Prolonged chest tube drainage or air leak after pulmonary resection	-	-	Sclerosis or additional tube thoracostomy indicated	Operative intervention indicated (e.g., thoracotomy with stapling or sealant application)	Life-threatening; debilitating; organ resection indicated	Death

Prolonged intubation after pulmonary resection (>24 hours after surgery)	-	-	Extubated within 24-72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Tracheostomy indicated	Death

Adverse Event	Short Name	1	2	3	4	5
Pulmonary fibrosis** (radiographic changes)	-	Minimal radiographic findings (or patchy or bi-basilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25-<50%	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50-<75%	Estimated radiographic proportion of total lung volume that is fibrotic is ≥75%; honeycombing	Death
Vital Capacity	-	90-75% of predicted value	<75-50% of predicted value	<50-25% of predicted value	<25% of predicted value	Death
Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	-	Mild or intermittent hoarseness or voice change, but fully understandable	Moderate or persistent voice changes, may require occasional repetition but understandable on telephone	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; requires voice aid (e.g., electrolarynx) for ≤50% of communication	Disabling; non-understandable voice or aphonic; requires voice aid (e.g., electrolarynx) for >50% written communication	Death
Pulmonary/Upper Respiratory – Other	-	Mild	Moderate	Severe	Life-threatening; disabling	Death

*A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have arisen.

**Fibrosis is usually a “late effect” seen >3 months after radiation or combined modality therapy (including surgery). It is thought to represent scar/fibrotic lung tissue. It may be difficult to distinguish from pneumonitis that is generally seen within 3 months of radiation or combined modality therapy.

APPENDIX II: QUALITY OF LIFE QUESTIONNAIRES

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: | | | | |

Your birthdate (Day, Month, Year): | | | | | | | | |

Today's date (Day, Month, Year): 31 | | | | | | | | |

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall <u>health</u> during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall <u>quality of life</u> during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31. How much did you cough?	1	2	3	4
32. Did you cough up blood?	1	2	3	4
33. Were you short of breath when you rested?	1	2	3	4
34. Were you short of breath when you walked?	1	2	3	4
35. Were you short of breath when you climbed stairs?	1	2	3	4
36. Have you had a sore mouth or tongue?	1	2	3	4
37. Have you had trouble swallowing?	1	2	3	4
38. Have you had tingling hands or feet?	1	2	3	4
39. Have you had hair loss?	1	2	3	4
40. Have you had pain in your chest?	1	2	3	4
41. Have you had pain in your arm or shoulder?	1	2	3	4
42. Have you had pain in other parts of your body?	1	2	3	4
If yes, where_____				
43. Did you take any medicine for pain? **1 No 2 Yes**				
If yes, how much did it help?	1	2	3	4

APPENDIX III: INSTRUCTIONS FOR NETWORK SITES

1. CONTACT INFORMATION

All questions related to the protocol or study implementation should be directed to:
Roswell Park Cancer Institute
CRS Network Office
ASB K 102B
Buffalo, New York 14263

Telephone:
716-845-8084 or 716-845-1203 - M-F; 8:00 AM to 5:30 PM
716-845-2300 - After hours, Weekends and Holidays: request the RPCI Principal Investigator
Fax: 716-845-8743

2. INFORMED CONSENT

- Informed Consent must be obtained by the **Investigator** from any patients wishing to participate, **prior to any procedures or change in their treatment**
- An informed consent template is provided by RPCI and can be amended to reflect institutional requirements
- All consent changes **must** be reviewed by Roswell Park Cancer Institute Network Office prior to submission to the site IRB.
- The informed consent must be IRB approved
- Always check that you are using the correct date and version of the IRB approved consent.

3. PATIENT REGISTRATION

The **Subject Enrollment Log** must be faxed to the CRS Network Office within 24 hours of the date the patient is consented. Once the Principal Investigator has determined that the eligibility criteria have been met, complete the **Patient Registration Form and fax it** to the RPCI Network Coordinator at (716) 845-8743.
Note: The patient completes the **Gender, Race, and Ethnicity form** and this is placed in the study binder.
Roswell Park Cancer Institute does not grant exceptions to eligibility criteria.

4. STUDY DEVIATIONS

- If a deviation has occurred to eliminate hazard, this should be reported to the RPCI Network, site IRB and any other regulatory authority involved in the trial.
- ANY study deviation will be recorded on the Study Deviation Log
- Patients who are inadvertently enrolled, with significant deviation(s) from the study- specified criteria, will be removed from the study
- Notify RPCI of any early patient withdrawal and appropriately document the discontinuation and the reason why.

5. STUDY DOCUMENTATION

- Study documents must be filled out completely and correctly. Ditto marks are not allowed.
- If an entry has been documented in error put a single line through the entry and initial and date the change. The auditor must be able to read what has been deleted.
    - Do NOT use white-out, magic marker, scratch-outs

- Do NOT erase entries
- Use only black ink for documentation on the accountability form and any other study forms.

6. DRUG ACCOUNTABILITY

Drug accountability will be strictly maintained, recording quantities of study drug received, dispensed to patients and wasted, lot number, date dispensed, patient ID number and initials, quantity returned, balance remaining, manufacturer, expiration date, and the initials of the person dispensing the medication.

- Responsibility rests solely with the Principal Investigator but can be delegated as appropriate (e.g. to pharmacy personnel)
- Records must be maintained regarding receipt, dispensing, return, waste and disposition of all investigational agents
- Study drug supply should only be used in accordance with the IRB approved study
- Drug accountability forms are protocol and agent specific, they are study source documents and will be used to verify compliance with the study
- Any discrepancies shall be documented and explained
- An inventory count should be performed with each transaction
- Drug accountability forms shall be stored with study related documents
- Each medication provided for this study and each dosage form and strength must have its own Drug accountability.
- Do **NOT** "transfer", "borrow" or "replace" supplies between studies
- Dispensing the wrong study supply is considered a **medication error**
- **Never** replace investigational agents with commercial product

7. SERIOUS ADVERSE EVENT REPORTING:

The site Investigator or designated research personnel will report all serious adverse events, whether related or unrelated to the study drug(s) to the **IRB in accordance with their local institutional guidelines.** The site will notify the CRS Network Office within one business day of being made aware of the SAE. A preliminary written report must follow within 24 hours (1 business day) of the oral notification using the following forms:

- SAE report form
- MEDWATCH 3500

A complete follow-up report must be filed within 10 working days.

8. UNANTICIPATED PROBLEM REPORTING:

An Unanticipated Problem (UAP) is any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given:
   (a) the research procedures that are described in the study- related documents, including study deviations, as well as issues related to compromise of patient privacy or confidentiality of data;
   (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized;

For all adverse events occurring that are unanticipated and related or possibly related to the research drug, biologic or intervention the participating physician or delegated research staff from each site will notify **their local IRB in accordance with their local institutional guidelines**. The site must also notify the CRS Network Office within 24 hours of being made aware of the Unanticipated Problem by completing the **RPCI Unanticipated Problem Report Form** and faxing it to the CRS Network office.

APPENDIX IV

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

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