Phase II trial of individualized lung tumor stereotactic ablative radiotherapy (iSABR)

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Contents

1. SYNOPSIS

Title of Study: Phase II trial of individualized lung tumor stereotactic ablative radiotherapy (SABR)

Study Phase: II

Study Center(s): Stanford University Hospitals and Clinic

Indication:

Stereotactic ablative radiotherapy (SABR) has emerged as an important and effective new treatment modality for lung tumors, but optimal dose regimens have not been fully established. Significant toxicity can be observed with the most commonly used dose regimens, implying that developing treatment regimens that optimize treatment based on tumor-specific factors could be of clinical benefit.

Primary Objective(s):

a. Evaluate local tumor control with individually optimized lung tumor SABR. Tumor control will be assessed by CT, PET-CT, and if appropriate, biopsy. The trial will focus on three cohorts: 1) patients with limited primary NSCLCs (T1aN0M0, T1bN0M0, T2aN0M0, T2bN0M0, or T3N0M0) non-small cell lung cancer; 2) patients with a history of NSCLC who have new limited primary NSCLC lesion(s); and 3) patients with more advanced lung cancer or lung metastases from a variety of different cancers.

Secondary Objective(s):

b. Evaluate the toxicity of individually optimized lung tumor SABR. Pulmonary, esophageal, chest wall, skin, vascular, cardiac/pericardial, and neurologic (brachial plexus/recurrent laryngeal/myelitis) toxicity will be scored by the CTCAE 4.0 criteria.
c. Evaluate the feasibility of anatomically optimized audio-visual biofeedback (AVB)-coached breath-hold technique assisted by fast delivery using gated RapidArc with flattening free filter mode (FFF) in a subset of patients. Feasibility will be assessed based on:
    i. The proportion of patients able to reproduce an anatomically-optimized breath-hold with AVB-coaching during treatment.
    ii. The reduction in treatment delivery time compared to gated free-breathing treatment.
d. Determine progression free, metastasis free, and overall survival in patients treated with individually optimized lung tumor SABR.
e. Examine new biomarkers in lung tumor SABR patients.

Hypothesis: We hypothesize that the therapeutic ratio of lung tumor SABR can be increased by (i) individual dosing based on tumor volume, and (ii) technologies to optimize the treatment anatomy by creating the greatest separation between target and critical normal organs at the time of treatment delivery.

Study Design:

We hypothesize that therapeutic ratio can be increased by:

i. Individualized dosing based on tumor volume. Our retrospective institutional data indicate that single fraction SABR is effective and safe for small volume pulmonary tumors but more intensive regimens are required to control larger tumors.
ii. Technologies to optimize the treatment anatomy by creating the greatest separation between target and critical normal organs at the time of treatment delivery. We will incorporate anatomically optimized AVB-coached breath-hold technique during image-guided gated RapidArc with FFF mode in a subset of patients, and evaluate its dosimetric impact compared to gated treatment during normal free-breathing.

We propose a prospective clinical trial to confirm the improved therapeutic ratio of individually optimized lung tumor SABR.

Primary and Secondary Endpoint(s):

Primary Endpoint

a. Local tumor control of individually optimized lung tumor SABR. This will be evaluated separately in the three different patient groups.

Secondary Endpoint

b. Toxicity of individually optimized lung tumor SABR.
c. Feasibility of anatomically optimized AVB-coached breath-hold technique assisted by fast delivery using gated RapidArc with FFF in a subset of patients. Feasibility will be based on the proportion of patients able to reproduce an anatomically-optimized breath-hold with AVB-coaching during treatment and the reduction in treatment delivery time compared to gated free-breathing treatment.
d. Progression free, metastasis free, and overall survival in patients treated with individually optimized lung tumor SABR.
e. Correlate plasma biomarkers with outcomes of lung tumor SABR patients (optional).

Number of Patients: The target accrual is 246 patients over 4 years (about 260 patients will be enrolled in the OnCore database due to study dropouts. NOTE: In a collaborative effort, some patients will be accrued at Shantou, CUHK, and Hokkaido Universities in China and Japan. We expect no more than 10 patients to be enrolled at each of these sites. Accrual at these sites will not increase the total number of patients enrolled.

Summary of Subject Eligibility Criteria:

Inclusion Criteria

- Limited primary NSCLCs (T1aN0M0, T1bN0M0, T2aN0M0, T2bN0M0, or T3N0M0) or metastatic lung tumors
- Up to 4 lesions may be included. For a single lesion the sum of three orthogonal diameters can be no more than 20 cm. For multiple lesions, no lesion can have a sum of orthogonal diameters greater than 15 cm.

- Both peripheral and central tumors are accepted for this trial.
- Age $\geq$ 18 years old
- Both men and women and members of all races and ethnic groups are eligible for this trial.

Exclusion Criteria

- Uncontrolled extrathoracic metastases
- Age < 18 years old
- Contraindication to receiving radiotherapy
- Women who are pregnant

Study Procedures:

i. Simulation: For a subset of patients, 4-D CT with AVB will be acquired with both natural and extreme tidal volume breathing. The sorted phase image from either scan demonstrating the largest separation between the target(s) and the specified organs at risk will be chosen for planning. Plan comparison with the natural end-exhale scan will be performed.

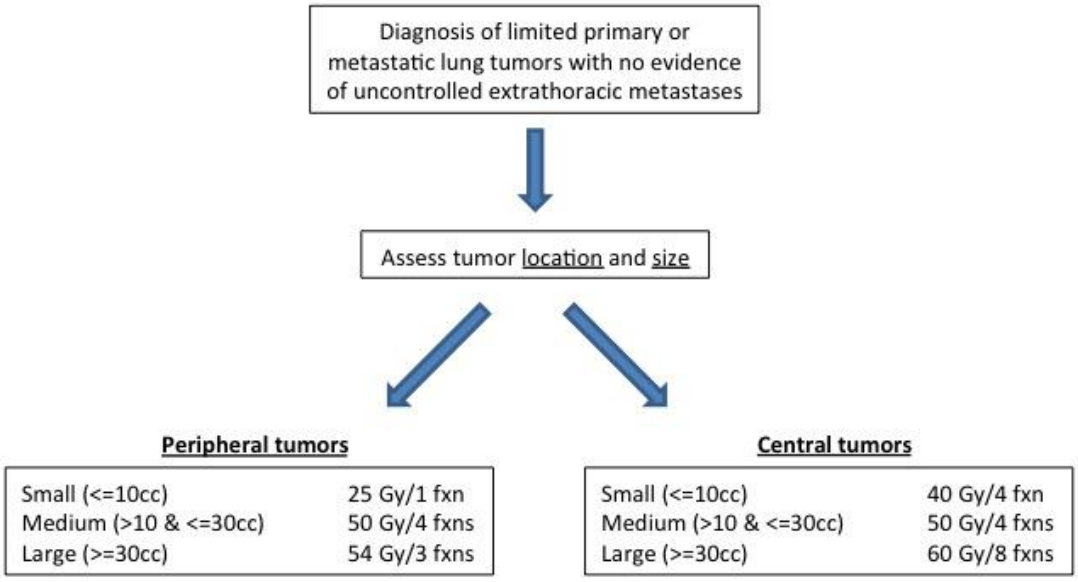
ii. Dose adaptation: Dosing will be based on tumor volume. Doses will be calculated using AAA (or Acuros XB when available). Conformity and normal tissue dose constraints will be specified in detail in the protocol.

iii. Pre-treatment verification and treatment delivery for AVB-coached breath-hold technique subgroup: Fluoroscopy and CBCT will be used to verify the ability of the patient to reproduce the targeted degree of breath hold with AVB assistance in a subset of patients.

Duration of Intervention and Evaluation: The study duration will be approximately 48 months for accrual, followed by 12 months of data analysis.

Statistical Methods: 246 patients will be enrolled. NOTE: About 260 patients will be enrolled in the OnCore database due to study dropouts.

2. SCHEMA


Diagnosis of limited primary or metastatic lung tumors with no evidence of uncontrolled extrathoracic metastases
Assess tumor location and size
Peripheral tumors
Small (<=10cc) 25 Gy/1 fxn
Medium (>10 & <=30cc) 50 Gy/4 fxns
Large (>=30cc) 54 Gy/3 fxns
Central tumors
Small (<=10cc) 40 Gy/4 fxn
Medium (>10 & <=30cc) 50 Gy/4 fxns
Large (>=30cc) 60 Gy/8 fxns

3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ANC	Absolute neutrophil count
AVB	Audiovisual Biofeedback
BED	Biologically Equivalent Dose
CBC	Complete Blood Count
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTV	Clinical Target Volume
DLCO	Diffusing capacity of the lung for carbon monoxide
DM	Distant Metastasis
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FEV-1	Forced expiratory volume in 1 second
FFF	Flattening Free Filter Mode
FNA	Fine needle aspirate
GTV	Gross tumor volume
IDN	Identification number
LC	Local control
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PFT	Pulmonary function test
PTV	Planning target volume
QOL	Quality of life
RC	Regional Control
RPM	Revolutions per minute
RTOG	Radiation Therapy Oncology Group
SABR	Stereotactic Ablative Radiotherapy
SBRT	Stereotactic body radiation therapy
XRT	External beam radiation therapy

4. OBJECTIVES

The primary objective is to evaluate the local control of individually optimized lung tumor SABR. Secondary objectives include evaluation of toxicity and evaluation of the feasibility of anatomically optimized AVB-coached breath-hold technique assisted by fast delivery using gated RapidArc with FFF in a subset of patients. Additional secondary objectives include determining progression free, metastasis free, and overall survival in patients treated with individually optimized lung tumor SABR.

5. BACKGROUND AND RATIONALE

5.1 Study Disease: Lung Cancer

Lung cancer is the leading cause of cancer mortality worldwide, accounting for over 1.3 million deaths each year, largely because it is most often diagnosed at advanced stages [1]. However, early stage non-small cell lung cancer (NSCLC) is often surgically curable with the appropriate resection, preferably lobectomy [2]. Unfortunately, a significant fraction of patients with early stage NSCLC cannot tolerate surgery owing to medical comorbidities. Similarly, while patients with pulmonary oligometastasis from malignancies at other sites may benefit from surgical resection [3], many have medical or technical contraindications to pulmonary resection [4].

5.2 Stereotactic Ablative Radiotherapy for Lung Cancer

In such patients, stereotactic ablative radiotherapy (SABR), also called stereotactic body radiation therapy (SBRT), has recently emerged as an important treatment option [5, 6]. A landmark prospective phase II clinical trial conducted by the Radiation Therapy Oncology Group, RTOG 0236, found that SABR resulted in outstanding local control (LC) and overall survival (OS) rates of 98% and 56% at 3 years in a cohort of strictly medically inoperable patients with peripherally located stage I NSCLC [7]. While treatment was well tolerated overall there was nevertheless a moderate incidence of significant (grade 3-4) toxicities. A prospective multi-institutional phase I/II trial of SABR for patients with 1-3 pulmonary metastases demonstrated similarly excellent 2-year LC of 96% [8].

Analyses of the dose-response relationships in SABR for both primary and metastatic lung tumors have demonstrated the importance of dose intensity [9-11], identifying a biologically effective dose (BED) of ≥100 Gy as a factor for achieving high rates of LC. In general these dose-response analyses have not been stratified by tumor volume. An earlier report from our institution of the initial results of a phase I dose escalation study using single fraction SABR for primary and metastatic lung tumor demonstrated 1 year LC of 91% using doses of >20 Gy [12]. A subsequent expanded analysis revealed that the critical factor for LC was tumor volume, such that in the dose range of

15-30 Gy in a single fraction, 11 month LC was 93-100% for tumors up to 12 mL but only 47% for tumors >12 mL [13]. Based on these observations we adopted a volume-adapted dosing strategy for lung tumor SABR in which patients with small tumors (<12 mL) were treated with single fraction regimens with BED <100 Gy while larger tumors (≥12 mL) were treated with more dose-intensive multi-fraction regimens with BED ≥100 Gy. The goal of this approach was to maintain equivalent LC while potentially reducing toxicities and improving convenience for patients with smaller tumors.

We have recently retrospectively analyzed lung tumor patients treated with the volume-adapted strategy. Median follow-up in this study was 13.5 months. LC at 12 months for smaller tumors treated with lower dose, single fraction regimens was 91.4% and for larger tumors treated with multi-fraction, higher dose regimens 92.5% (p=0.24). For primary lung tumors only (excluding metastases), LC was 92.6% and 91.7%, respectively (p=0.58). RC, freedom from DM and OS did not differ significantly between the groups. Rates of radiation pneumonitis, chest wall toxicity, and esophagitis were low in both groups, but all grade 3 toxicities developed in Group 2 (p=0.02).

Based on this experience, we propose a prospective phase 2 clinical trial of tumor volume adapted dosing for SABR of pulmonary tumors. The primary endpoints will be LC and toxicity. Our hypothesis is that an individualized regimen will result in high local tumor control across strata of tumor volumes, while toxicity can be minimized by avoiding the need for the most dose intensive regimens in most patients.

We will include three cohorts for analysis, each with 82 patients. The first cohort (1A) will consist of patients with Stage I non-small cell lung cancer. The second cohort (1B) will consist of patients with multiple primary non-small cell lung cancer. The third cohort (II) will consist of patients with lung metastases from a variety of different cancers.

5.3 Audio-visual Biofeedback

In addition, unique technological features of the Varian TrueBeam STX system for SABR, particularly the very rapid treatments afforded by RapidArc using the flattening filter free (FFF) mode, make possible novel treatment approaches. While margins can be reduced by the use of respiratory gating, the long treatment delivery times using conventional dose rates and field arrangements necessitate treating during natural free breathing. However, fast treatments could in theory be completed in a small number of breath holds, which would then not be restricted to the natural breathing range but could be at extremes of tidal volume. It would then be possible to select a degree of breath hold that is anatomically-optimized, creating the greatest separation between the target and critical organs at risk. Of note, at 1400 MU/min in 6X FFF mode, a 25 Gy fraction could be delivered in less than 3.5 minutes of beam-on time, or ~15 breath holds even in a patient with compromised pulmonary function.

We propose in this trial to use audio-visual biofeedback to enable patients to reproduce anatomically-optimized breath-holds to achieve plans producing the highest possible separation between the tumor and the organs at risk. We will evaluate the feasibility of this approach, as assessed by the proportion of patients able to reliably reproduce the anatomically-optimized breath-holds with AVB-coaching, and the reduction in treatment delivery time compared to treatment during free-breathing. We will also evaluate the dosimetric impact of the anatomically-optimized approach compared to conventional free-breathing treatment gated at natural end-exhale.

5.4 Rationale for Study

Stereotactic ablative radiotherapy (SABR) has emerged as an important and effective new treatment modality for lung tumors, but currently many different dose regimens are used and optimal regimens remain to be established. Significant toxicity can occur with the most effective published regimens, indicating that the therapeutic ratio could be further improved.

We hypothesize that therapeutic ratio can be increased by:

i. Individualized dosing based on tumor volume. Our institutional data indicate that single fraction SABR is effective and safe for small volume pulmonary tumors but more intensive regimens are required to control larger tumors.
ii. Technologies to optimize the treatment anatomy by creating the greatest separation between target and critical normal organs at the time of treatment delivery. We will incorporate anatomically optimized AVB-coached breath-hold technique during image-guided gated RapidArc with FFF mode, and evaluate its dosimetric impact compared to gated treatment during normal free-breathing.

We propose a prospective clinical trial to confirm the improved therapeutic ratio of individually optimized lung tumor SABR. At our institution about 70 patients per year with lung tumors are treated with SABR, and essentially all would benefit from the knowledge gained from this study. Thousands of patients per year worldwide stand to benefit as well. Our approach would allow individualization of therapy for the maximum efficacy with the least toxicity.

5.5 Correlative Studies Background

Blood-based biomarkers hold great promise as diagnostic markers indicative of disease state and predictors outcomes in lung tumor patients. A variety of biomarkers have been investigated in patients with lung tumors, including protein, DNA, and miRNA

biomarkers. Cell-free DNA (cfDNA) is a particularly intriguing biomarker in this patient population [14]. Tumors continually release DNA into the circulation through incompletely understood mechanisms that appear to involve both apoptosis and necrosis [15]. Previous studies have indicated that NSCLC patients have statistically significantly higher levels of cfDNA in the circulation than unaffected controls [16]. Furthermore, cfDNA levels have been shown to decrease after effective treatment in a variety of tumors, indicating that they can be used to assess dynamics of treatment response [15].

We plan to measure plasma levels of cfDNA in patients prior to initiating treatment and at each follow-up visit. We hypothesize that changes in cfDNA concentration will be predictive of outcome in this group of patients.

Additional biomarkers may also be assessed.

6. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

6.1 Inclusion Criteria

- Limited primary NSCLCs (T1aN0M0, T1bN0M0, T2aN0M0, T2bN0M0, or T3N0M0) or metastatic lung tumors with no evidence of uncontrolled extrathoracic metastases.
- Up to 4 lesions may be included. For a single lesion the sum of three orthogonal diameters can be no more than 20 cm. For multiple lesions, no lesion can have a sum of orthogonal diameters greater than 15 cm.
- Both peripheral and central tumors are accepted for this trial.
- Age > = 18 years old
- Both men and women and members of all races and ethnic groups are eligible for this trial.
- Note: Patients may be enrolled more than once (eg, for a new tumor)

6.2 Exclusion Criteria

- Evidence of uncontrolled extrathoracic metastases
- Contraindication to receiving radiotherapy
- Age < 18 years old. Children are excluded because lung malignancies rarely occur in this age group. Furthermore, treatment requires a great deal of patient cooperation including the ability to lie still for several hours in an isolated room.
- Pregnant and breastfeeding women are excluded; as well as women of child-bearing potential who are unwilling or unable to use an acceptable method of birth control (hormonal or barrier method of birth control; abstinence) to avoid pregnancy for the duration of the study. Male subjects must also agree to use

effective contraception for the same period as above. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

- Prior radiation therapy is allowed but there should not be overlap with the prior high dose regions unless approved by the protocol directors.

6.3 Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

7. TREATMENT PLAN

7.1 Study Design/Schedule

- This is a prospective phase II study.
- Patients with primary lung cancer or metastasis to the lung with no evidence of uncontrolled extrathoracic metastasis will be enrolled on this study.

7.2 Procedures: SABR Administration and Radiation Treatment Planning

7.2.1 Pre-SABR Tests, Procedures, and Planning

The following will be completed prior to SABR:

a) Medical history and clinical examination.
b) CBC (optional). Additionally, up to 50 ml of blood may be drawn for research in Dr. Diehn's laboratory; blood may also be collected at post-treatment follow-up visits. At most, the lesser of 50 ml or 3 ml per kg will be collected for research purposes in an 8 week period. For specific information regarding collection and processing, see Section *8 Correlative Studies*.
c) Pathologic confirmation of malignancy whenever possible. (This will generally be accomplished using CT-guided or bronchoscopic biopsies.) If consent is provided by the patient, tumor tissue for research may be obtained. If pathologic confirmation is not possible, a target lesion must be a non-calcified pulmonary nodule or lymph node that is present on at least 3 imaging studies (can include simulation scan). The nodule must have increased in size or proportion of solid component on CT and/or show increased FDG uptake on PET over at least 2 imaging studies.
d) FDG-PET/CT and thoracic CT scan with contrast (recommended).

e) Signed informed consent document.
f) Permission from patient for future postmortem examination (optional).

7.2.2 Fiducials

We will implant peri-tumoral metallic fiducial markers for image-guided tumor localization as needed, generally for lower lobe locations where the magnitude of tumor motion tends to be greatest. The fiducials will be used as surrogates for targeting the daily tumor position during treatment. The fiducials will be placed directly into the tumor and/or periphery under CT guidance. Fiducials may be implanted prior to enrollment as this is an acceptable standard of care procedure for any patient receiving SABR for lung tumors.

7.2.3 Simulation

During radiotherapy simulation, customized immobilization devices will be formed for each patient, and 4-dimensional CT (4-D CT) and PET-CT will be acquired in the treatment position.

7.2.4 Treatment planning

The treating physicians will contour the gross tumor volume (GTV) on axial CT slices using lung windows for visualizing tumor/lung interfaces and mediastinal windows for tumor/soft tissue interfaces, with the aid of fused PET. No explicit expansion for microscopic extension will be added to form the clinical target volume (CTV), i.e., CTV=GTV. Breathing-induced tumor motion will be assessed using the 4-D CT data and managed by respiratory gating, dynamic tumor tracking, or motion-inclusive technique, and the internal target volume (ITV) will be designed accordingly. A 0.5 cm setup margin will be added to the ITV to form the final planning target volume (PTV).

Treatment will be delivered using any suitable linear accelerator with image-guidance capabilities. Dose calculations should be heterogeneity corrected using an accurate algorithm (pencil beam not acceptable).

7.2.5 SABR Treatment Delivery:

<u>Presciption doses for peripheral tumors (except colorectal cancer metastases)</u>:

Peripheral tumors are tumors that do not meet the definition for central tumors described below. Volume-adapted dose prescriptions for peripheral tumors will be as follows:

Tumor volume	Peripheral dose (covering 95% of PTV)	Maximum dose (centered in GTV) of at least:
<=10	25 Gy / 1 fraction	30 Gy /1 fraction
>10 and <=30	50 Gy / 4 fractions	60 Gy / 4 fractions
>30	54 Gy / 3 fractions	64.8 Gy / 3 fractions

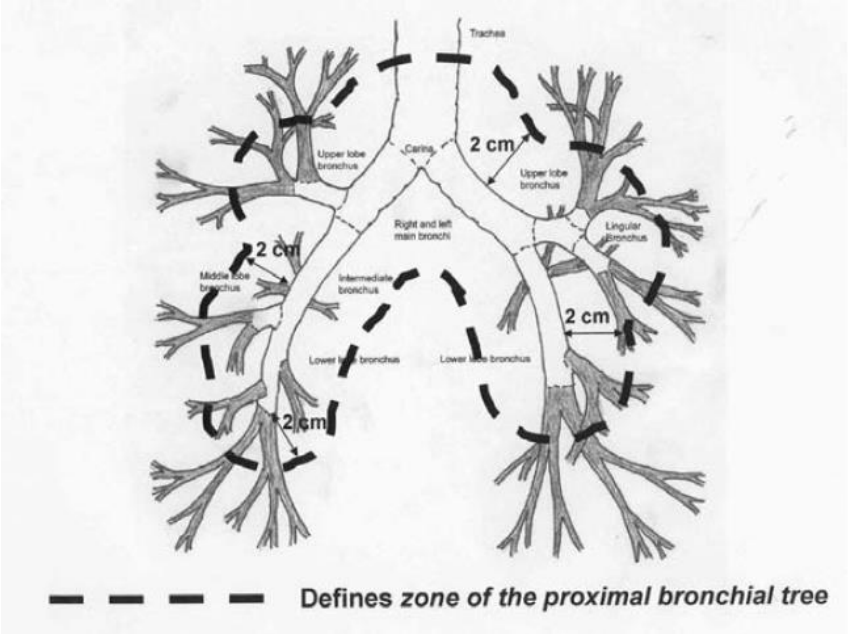
Prescription doses for peripheral colorectal cancer metastases:

Retrospective analyses of our own data as well as published results from other institutions indicated that colorectal cancers appear to be relatively radioresistant. Particularly, we noted high rates of local failure in colorectal cancer metastases to the lung in tumor that received 25 Gy in one fraction. Therefore, volume-adapted dose prescriptions for peripheral colorectal cancer tumors will be as follows:

Tumor volume	Peripheral dose (covering 95% of PTV)	Maximum dose (centered in GTV) of at least:
<=10	50 Gy / 4 fraction	60 Gy /4 fraction
>10 and <=30	50 Gy / 4 fractions	60 Gy / 4 fractions
>30	54 Gy / 3 fractions	64.8 Gy / 3 fractions

Central tumors:

Central tumors are defined as having their GTV within or touching the zone of the proximal bronchial tree or near critical central structures. The zone of the proximal bronchial tree is defined as a volume 2 cm in all directions around the proximal bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus right and left lower lobe bronchi). [See figure below] For the purposes of this protocol central tumors include those within 2 cm of the zone of the proximal bronchial tree. Alternatively, tumors whose PTV overlaps major vessels (aorta or superior vena cava), esophagus, heart, trachea, pericardium, or brachial plexus will also be considered central.



Prescription doses for central tumors (except colorectal cancer metastases):

Volume-adapted dose prescriptions for central tumors will be as follows:

Tumor volume (mL)	**Peripheral dose (covering 95% of PTV)**	**Maximum dose (centered in GTV) of at least:**
<=10	40 Gy / 4 fractions	48 Gy / 4 fractions
>10 and <=30	50 Gy / 4 fractions	60 Gy / 4 fractions
>30	60 Gy / 8 fractions	72 Gy / 8 fractions

Prescription doses for central colorectal cancer metastases:

Volume-adapted dose prescriptions for central colorectal cancer tumors will be as follows:

Tumor volume (mL)	**Peripheral dose (covering 95% of PTV)**	**Maximum dose (centered in GTV) of at least:**
<=10	50 Gy / 4 fractions	60 Gy / 4 fractions
>10 and <=30	50 Gy / 4 fractions	60 Gy / 4 fractions
>30	60 Gy / 8 fractions	72 Gy / 8 fractions

Prescription Dose Constraints and Conformality

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 (PTV V95%RX = 100%). The global maximum dose point should be within the PTV and ideally within the GTV. The maximum dose within the GTV should be at least 120% of the prescription dose (as indicated in tables above). The minimum dose to the GTV should be at least 100% of the prescription dose (specifically, no more than 0.035 mL of the GTV should receive less than 100% of the prescription dose, with a tolerance of 2.5%).

Conformality parameters: Treatment plans should be as conformal as possible. For tumors located far from critical structures, a very conformal distribution should be obtained. For tumors very close to critical structures, dose distributions may be somewhat asymmetric, with a sharper fall-off on the side(s) of the tumor that are closest to the critical structure(s) at risk. The following conformality criteria must be met:

GTV volume (mL)	**Ratio of Prescription Isodose Volume to the PTV Volume**		**Maximum Dose @ 2 cm from PTV (in % of dose prescribed)**	
	Ideal	**Required**	**Ideal**	**Required**
<=10	<1.2	<1.5	<55	<65
>10 and <=30	<1.2	<1.5	<64	<82
>30	<1.2	<1.5	<72	<90

Critical organ dose constraints

The following tables list dose constraints to critical structures based on the number of fractions prescribed. Exceeding these dose limits by more than 5% constitutes an unacceptable protocol deviation.

Single fraction treatment:

Critical structures with absolute volume and absolute point dose limits:
Exceeding any of these limits constitutes a major protocol violation.

Critical structure	**Volume dose limits (1 fraction)**		**Maximum Point dose limit (<0.035 mL)**
	Dose	**Volume**	**Dose**
Spinal cord	10 Gy 7 Gy	<0.35 mL <1.2 mL	14 Gy

Brachial plexus	14 Gy	<3 mL	17.5 Gy
Skin	23 Gy	<10 mL	26 Gy
Lungs-GTV	7.4 Gy 7 Gy 20 Gy	<1000 mL <1500 mL <10% (require <15%)	NA
Stomach	11.2 Gy	<10 mL	12.4 Gy
Small bowel*	11.2 Gy 9 Gy	<5 cc <10 cc	12.4 Gy

Critical structures with <u>relative</u> volume and <u>absolute</u> point dose limits: The volume dose limits are suggested limits for these structures. Exceeding these limits is not a protocol violation. The recommended maximum point dose limits are also suggested limits that may not be met. However, exceeding any of the required maximum point dose limits constitutes a major violation.

Critical structure	**Volume dose limits (1 fraction)**		**Maximum point dose limit (<0.035 mL)**	
	Dose	**Volume**	**Recommended**	**Required**
Esophagus*	11.9 Gy	<5 mL	15.4 Gy	105% of PTV prescription dose
Heart/pericardium	16 Gy	<15 mL	22 Gy	105% of PTV prescription dose
Great vessels*	25 Gy	<10 mL	25 Gy	105% of PTV prescription dose
Trachea and ipsilateral bronchus*	10.5 Gy	<4 mL	20.2 Gy	105% of PTV prescription dose
Chest wall#	18 Gy	<10cc (<30cc required)	NA	105% of PTV prescription dose
Liver	9.1 Gy	<700 mL	NA	105% of PTV prescription dose

***** Avoid circumferential radiation
# Chest wall limits may be exceeded for an otherwise excellent plan. This will not be considered a violation.

Three fraction treatment:

Critical structures with absolute volume and absolute point dose limits: Exceeding any of these limits constitutes a major protocol violation.

Critical structure	**Volume dose limits (3 fractions)**		**Maximum Point dose limit (<0.035 mL)**
	Dose	**Volume**	**Dose**
Spinal cord	18 Gy 12.3 Gy	<0.35 mL <1.2 mL	21.9 Gy
Brachial plexus	20.4 Gy	<3 mL	24 Gy
Skin	30 Gy	<10 mL	33 Gy
Lungs-GTV	11.4 Gy 10.5 Gy 20 Gy	<1000 mL <1500 mL <10% (require <15%)	NA
Stomach	16.5 Gy	<10 mL	22.2 Gy
Small bowel*	16.5 Gy 11.4 Gy	<5 cc <10 cc	22.2 Gy

Critical structures with relative volume and absolute point dose limits: The volume dose limits are suggested limits for these structures. Exceeding these limits is not a protocol violation. The recommended maximum point dose limits are also suggested limits that may not be met. However, exceeding any of the required maximum point dose limits constitutes a major violation.

Critical structure	**Volume dose limits (3 fractions)**		**Maximum point dose limit (<0.035 mL)**	
	Dose	**Volume**	**Recommended**	**Required**
Esophagus*	17.7 Gy	<5 mL	25.2 Gy	105% of PTV prescription dose

Heart/pericardium	24 Gy	<15 mL	30 Gy	105% of PTV prescription dose
Great vessels*	39 Gy	<10 mL	45 Gy	105% of PTV prescription dose
Trachea and ipsilateral bronchus*	15 Gy	<4 mL	30 Gy	105% of PTV prescription dose
Chest wall#	30 Gy	<10cc (<30cc required)	NA	105% of PTV prescription dose
Liver	17.7 Gy	<700 mL	NA	105% of PTV prescription dose

***** Avoid circumferential radiation

Chest wall limits may be exceeded for an otherwise excellent plan. This will not be considered a violation.

Four fraction treatment:

Critical structures with absolute volume and absolute point dose limits:
Exceeding any of these limits constitutes a major protocol violation.

Critical structure	**Volume dose limits (4 fractions)**		**Maximum Point dose limit (<0.035 mL)**
	Dose	**Volume**	**Dose**
Spinal cord	20.8 Gy 13.6 Gy	<0.35 mL <1.2 mL	26 Gy
Brachial plexus	23.6 Gy	<3 mL	27.2 Gy
Skin	33.2 Gy	<10 mL	36 Gy
Lungs-GTV	12.4 Gy 11.6 Gy 20 Gy	<1000 mL <1500 mL <10% (require <15%)	NA
Stomach	17.6 Gy	<10 mL	27.2 Gy

Small bowel*	17.6 Gy 12 Gy	<5 cc <10 cc	27.2 Gy

Critical structures with <u>relative</u> volume and <u>absolute</u> point dose limits: The volume dose limits are suggested limits for these structures. Exceeding these limits is not a protocol violation. The recommended maximum point dose limits are also suggested limits that may not be met. However, exceeding any of the required maximum point dose limits constitutes a major violation.

Critical structure	**Volume dose limits (4 fractions)**		**Maximum point dose limit (<0.035 mL)**	
	Dose	**Volume**	**Recommended**	**Required**
Esophagus*	18.8 Gy	<5 mL	30 Gy	105% of PTV prescription dose
Heart/pericardium	28 Gy	<15 mL	30 Gy	105% of PTV prescription dose
Great vessels*	43 Gy	<10 mL	49 Gy	105% of PTV prescription dose
Trachea and ipsilateral bronchus*	15.6 Gy	<4 mL	34.8 Gy	105% of PTV prescription dose
Chest wall#	33.6 Gy	<10cc (<30cc required)	NA	105% of PTV prescription dose
Liver	19.2 Gy	<700 mL	NA	105% of PTV prescription dose

***** Avoid circumferential radiation

Chest wall limits may be exceeded for an otherwise excellent plan. This will not be considered a violation.

<u>Eight fraction treatment:</u>

Critical structures with <u>absolute</u> volume and <u>absolute</u> point dose limits: Exceeding any of these limits constitutes a major protocol violation.

Critical structure	Volume dose limits (8 fractions)		Maximum Point dose limit (<0.035 mL)
	Dose	Volume	Dose
Spinal cord	27.2 Gy 16.8 Gy	<0.35 mL <1.2 mL	36 Gy
Brachial plexus	32.8 Gy	<3 mL	36.8 Gy
Skin	40.8 Gy	<10 mL	44.8 Gy
Lungs-GTV	14.4 Gy 13.6 Gy 20 Gy	<1000 mL <1500 mL <10% (require <15%)	NA
Stomach	20 Gy	<10 mL	36.8 Gy
Small bowel*	20 Gy 13.6 Gy	<5 cc <10 cc	36.8 Gy

Critical structures with <u>relative</u> volume and <u>absolute</u> point dose limits: The volume dose limits are suggested limits for these structures. Exceeding these limits is not a protocol violation. The recommended maximum point dose limits are also suggested limits that may not be met. However, exceeding any of the required maximum point dose limits constitutes a major violation.

Critical structure	Volume dose limits (8 fractions)		Maximum point dose limit (<0.035 mL)	
	Dose	Volume	Recommended	Required
Esophagus*	21.6 Gy	<5 mL	40 Gy	105% of PTV prescription dose
Heart/pericardium	36.9 Gy	<15 mL	39.7 Gy	105% of PTV prescription dose
Great vessels*	57.7 Gy	<10 mL	65 Gy	105% of PTV prescription dose
Trachea and	19.8 Gy	<4 mL	46.4 Gy	105% of PTV

ipsilateral bronchus*				prescription dose
Chest wall#	43.4 Gy	<10cc (<30cc required)	NA	105% of PTV prescription dose
Liver	23.2 Gy	<700 mL	NA	105% of PTV prescription dose

***** Avoid circumferential radiation

Chest wall limits may be exceeded for an otherwise excellent plan. This will not be considered a violation.

7.3 Duration of Follow-Up

Upon completion of SABR, study follow up will include serial imaging (CT scans and/or PET/CT if possible and as deemed necessary), detailed medical history, physical examination and quality of life assessment every 3 months for 1 year (+/- 4 weeks). Thereafter all patients are considered to be off study treatment and will be followed for progression and survival outcomes collected during standard of care visits. Typically this includes imaging studies, history and physical examinations every 6 months for 2 years, then annually. Follow up intervals may also be more frequent as indicated clinically. A complete blood count (CBC) (optional), tumor marker studies (optional), history/physical, CT and/or PET/CT (optional) will be performed at each follow-up interval until death. PFTs (optional) with DLCO and FEV-1 will be obtained 6 and 12 months post-SABR then once annually. Separate samples of blood may be drawn at the time of follow-up visits, studies, and/or laboratory draws and retained for research efforts to develop novel blood biomarkers.

Patients will remain enrolled on this protocol until there is evidence that their disease has progressed either locally or distantly. Patients whose disease has progressed either locally or distantly and get treated for the progression during the 1-year of active follow-up will be taken off the study. We will continue to obtain follow up information for 3 years after RT.

7.4 Criteria for Removal from Study

Patients may be removed at any time from the study at their request. Additionally, patients who are unable to cooperate with obtaining the protocol studies will be withdrawn. Patients in whom usable imaging studies are not attainable or who can't be reproducibly positioned at the time of treatment will also be withdrawn. Withdrawals will be replaced to achieve the target accrual.

7.5 Alternatives

This study is optional, so the only alternative is to not participate in this study.

7.6 Compensation

Patients will not be paid. Costs of protocol studies will be paid through protocol funding, and patients will not incur additional costs due to their participation.

8. CORRELATIVE STUDIES

8.1 Analysis of patient plasma for biomarker development.

Collection of Specimen(s) (optional):

Patients will elect whether they want to participate in this portion of the study on the consent form.

Blood Samples

a) Blood (EDTA preserved) for research purposes may be drawn prior to radiation treatment and at follow-up visits, studies, or blood draws. For each collection, up to 50 ml will be drawn (purple/violet tubes).

b) Immediately, after collection, blood will be centrifuged at 3000 RPM for 10 minutes at 4°C and plasma collected. The supernatant will be aliquoted for storage at -80°C. The pellet containing (white and red blood cells) will also be stored in a separate tube at -80°C.

Tumor Biopsy Tissue Samples

a) Consent for obtaining tumor samples: All patients with a presumed diagnosis of malignancy within the lung can give consent or decline consent to obtain an additional tumor tissue for research purposes. In this situation, the research biopsy should be obtained only after a final diagnosis (preliminary if determined by the pathologist during the diagnostic biopsy) of malignancy has been reached by the pathologist. Once a preliminary/final diagnosis has been obtained, fiducials can be placed into the tumor for tumor tracking. In the event the patient already has a confirmed pathologic diagnosis of cancer in the lung, a repeat biopsy procedure (usually CT-guided) may be performed to obtain tissue with/or without simultaneous placement of fiducials.

b) Tumor sample processing: Fine needle aspirations (FNA) and core biopsies (if possible) of tumor tissue will be immediately placed into small twist tubes that can be

stored at -80°C. Sample tubes are immediately immersed into a canister of liquid nitrogen with forceps/tube holder until completely frozen. Samples are then transferred into a -80°C freezer for storage.

c) Consent for use of left over diagnostic specimens: All patients with a presumed diagnosis of malignancy within the lung can give consent or decline consent to allow left over biological materials from diagnostic procedures (e.g. paraffin-embedded tissues, DNA, frozen tissues) to be used for research purposes.

8.2 Coding of specimens for privacy protection

At the time of enrollment each patient will be given a specific confidential identification number (IDN). Specimens will be stored under the patient's IDN. The information can be shared with other investigators listed on this protocol. Study data will be maintained in password protected computer files (protected online database). Only research personnel will have access to this information.

9. STUDY CALENDAR

	Pre-Registration Timeframes are in weeks prior to registration	**Pre-Treatment** Timeframes are in weeks prior to treatment	**Follow-Up (Post SABR): Every 3 mos. for 1 year (+/- 4 weeks); then follow-up for progression and survival outcomes**
Histologic confirmation (strongly encouraged but not required when clinical suspicion of malignancy is high) #	X		
History/physical	Within 12 weeks		X
Performance Status and Weight #		Within 8 weeks	X
CT scan of thorax with or without contrast (with contrast is preferable)*	Within 8 weeks		X
FDG PET*	Within 8 weeks		Optional but encouraged.
PFTs, including DLCO, FEV1, and FVC #^		Within 12 weeks	6,12 months post-SABR then yearly

CBC w/ diff & ANC #^		Within 4 weeks	X
Urine or Serum pregnancy test (if applicable)		Within 3 days	
Tumor response evaluation			X
Adverse event evaluation			X
Tissue for banking and blood for translational research (if patient consents) #		X	
QOLs #		X	X

Encouraged but not required
^ PFTs and CBC are used as baseline measures. Ideally, they should be obtained prior to treatment, but at the latest they can be obtained by the completion of treatment.
* CT and PET/CT scans obtained at the time of simulation are acceptable. PET is not required if tumor is known to be PET negative from prior scans, or for oligometastatic tumors of non-lung primary.

10. MEASUREMENT OF ENDPOINT

10.1 Anti-tumor Effect

Patients will be evaluated for anti-tumor effect by follow-up imaging (lung protocol CT and/or PET-CT imaging) as outlined above. Lung protocol CT scans (biphasic imaging, 1.25 mm cuts) and/or FDG PET-CT scans will be obtained at all follow-up intervals as described in the treatment calendar. All subsequent scans (post-treatment) will be compared to the same pretreatment CT or PET/CT that was used in conjunction with radiation treatment planning.

10.2 Definitions

Patients will be evaluable for toxicity and evaluable for objective response at the follow-up intervals specified above.

Local Failure refers to either primary tumor failure or involved lobe failure or both. Failure will be documented by biopsy when possible and otherwise will be defined as radiographic progression on CT and/or PET/CT that leads to a change in management, including institution of chemotherapy, re-irradiation, etc. The criteria for time to progression and progression-free survival (PFS) will be the duration from SABR treatment to documented local/regional or distant progression or death. Local PFS will be the duration from SABR treatment to local progression or death from any cause.

11. DATA REPORTING/REGULATORY CONSIDERATIONS

11.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Center Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

11.2 Data and Safety Monitoring Plan

The Stanford Cancer Center Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

11.2.1 Data Monitoring Plan for International Sites

The data monitoring plan for the iSABR international sites has six components:

11.2.1.1 Local GCP and human subjects protection training

The coordinators at each site will undergo training in Good Clinical Practice and human subjects protection and will email their completion certificates to the Stanford coordinator.

11.2.1.2 Local delegation logs

The Stanford coordinator will send a delegation log to each site, to be filled out with the names, signatures, and roles of all personnel working on the iSABR international study. Once complete, the delegation logs will be emailed back to the Stanford coordinator.

11.2.1.3 Initial OnCore and Redcap training session via BlueJeans

The Stanford coordinator will create a BlueJeans training session on how to register patients in OnCore and fill out case report forms (CRFs) in Redcap. The BlueJeans training session will be held before each site starts enrolling patients on the study. All sites will fill out the forms in English. **Important:** When the local coordinator is working in OnCore or Redcap, he or she will only be able to see local data, not Stanford data or data from the other international sites.

11.2.1.4 Regular training on protocol amendments

Any time an amendment is made to the iSABR protocol, the Stanford coordinator will communicate the change to all sites via email or a BlueJeans session if needed. The sites will then have the amended protocol approved by the local IRB.

11.2.1.5 Remote monitoring during the study

As described earlier in this document, all data recording and storage will be in English. However, at Shantou medical documentation is in Chinese and at Hokkaido it is in Japanese. At CUHK, some medical documentation may be in English. Coordinators at all three sites will attach source documents in Redcap so that the Stanford coordinator can monitor and verify that patients have been screened correctly for eligibility and that the data is correct and complete. At Shantou and CUHK, the source documents will be translated into English first before they are sent to Stanford.

11.2.1.6 SAE Reporting

Serious adverse events (SAEs) will be reported by the international sites to (a) the local IRBs and (b) the Stanford coordinator. The Stanford coordinator will provide the international sites with SAE reporting paperwork. Once SAE paperwork has been delivered to Stanford, the Stanford coordinator will submit it to the Cancer Clinical Trials Office (CCTO) to be recorded in OnCore.

11.3 Data Management Plan

The Protocol Director, or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document treatment outcomes for data

analysis. Case report forms will be developed using paper documents. CRFs will be kept in a locked cabinet, only accessible to the research team.

11.3.1 **Overview of Data Management at Stanford**

Data on the iSABR study at Stanford is managed via three components:

a. OnCore

Patients are registered and reported to the NCI through OnCore, a web-based database application. Patients are registered in OnCore within 5 days after signing the consent form. Patients are numbered consecutively.

b. Redcap

Case report forms (CRFs) are filled and stored electronically in Redcap, a web-based database application. Patients are numbered consecutively using the same numbers as in OnCore. The CRFs include a Baseline Evaluation Form, Registration Form, Treatment Summary Form, and Follow-Up Form. One Follow-Up Form is filled out for each patient follow-up visit, so several Follow-Up Forms are filled out for each patient over the course of the study. The Follow-Up Form records local, regional, and distant control provided by the iSABR treatment. It also records any adverse events experienced by the patient. Common adverse events such as esophagitis and pneumonitis are recorded using radio buttons. Other adverse events can be typed into a Comments box.

c. Document binders

Key documents are stored as hardcopy in patient binders. Key documents include:

A. The signed informed consent form
B. The eligibility checklist and source documents required to prove eligibility (history and physical, pathology, and CT or PET/CT scan) as well as documentation of optional tests used as baseline measures (pulmonary function tests, complete blood count)
C. The Treatment Summary written by the treating physician
D. Follow-up visit notes written by the treating physician
E. Documentation of any serious adverse events (SAEs)

There is some redundancy between Redcap and the document binders. Specifically, the Redcap Registration Form mirrors the eligibility checklist, the Treatment Summary Form captures key information from

the physician's Treatment Summary, and the Follow-Up Forms capture key information from the follow-up visit notes.

11.3.2 Sponsorship of Coordinators at the International Sites

[redacted]

11.3.3 Overview of Data Management for the International Sites

When the iSABR study expands to the three international sites (Shantou, CUHK, and Hokkaido), the same three components of data management will be used as described above.

a. OnCore

The NCI requires multi-site patients to be reported in OnCore: even though they are not Stanford patients, they are involved in Stanford's research activities. The Stanford clinical research coordinator (CRC) will provide training in OnCore to the research teams as described in the data monitoring plan, above. Patients will be registered in OnCore at the international sites within 5 days of signing the consent form, as they are at Stanford. The numbering scheme will be as follows for the three sites:

- SHAN-001, SHAN-002, SHAN-003…. for Shantou University patients
- CUHK-001, CUHK-002, CUHK-003…. for Chinese University at Hong Kong patients
- HOKK-001, HOKK-002, HOKK-003…. for Hokkaido University patients

b. Redcap

Redcap has a Data Access Groups (DAGs) feature that allows separate teams to share a database without viewing each other's data. The Stanford coordinator will provide training in Redcap to the PIs and coordinators as described in the data monitoring plan, above. The numbering scheme will be the same as in OnCore:

- SHAN-001, SHAN-002, SHAN-003…. for Shantou University patients
- CUHK-001, CUHK-002, CUHK-003…. for Chinese University at Hong Kong patients

- HOKK-001, HOKK-002, HOKK-003…. for Hokkaido University patients

Note that in Redcap it will be necessary to manually enter the international ID in the "International ID" field at the top of the Baseline Evaluation Form. The ID number that is auto-generated by Redcap will not be used.

NOTE: Coordinators at the international sites will upload source documents into Redcap so that these documents can be translated at Stanford to monitor whether information has been recorded correctly in the Redcap database. See "Remote monitoring during the study," above.

c. Document binders

Document binders will be kept at the international sites for international patients enrolled on the iSABR study. Whenever a new patient is enrolled at a subsite, a document binder will be created for that patient just as it is at Stanford. The Stanford coordinator will instruct the international research teams on how to create a patient binder.

11.4 Evaluation for Adverse Events

Toxicity will be scored according to the NCI CTCAE v4.0 (Appendix II).

Serious adverse events (SAE's) will be reported to the Stanford PI and to the IRB, and DSMC as per the Cancer Clinical Trials Office Standard Operating Procedure for SAE reporting. All SAEs will be reported while on study and will be monitored for up to one year after the last dose of the study treatment is given.

Definition of adverse event: any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

Definition of serious adverse event: any adverse experience that results in any of the following outcome: death, a life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event when, based upon medical judgment, they may jeopardize the patient or

subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Definition of unanticipated problems involving risks to participants or others (UPs): events (including internal or external events, death, life-threatening experiences, injuries, breaches of confidentiality, or other problems) that occur any time during or after the research study, which in the opinion of the PD are:

1. Unexpected - not in the consent form, protocol, package insert, or label; or unexpected in its frequency, severity, or specificity, AND
2. Related to the research procedures – caused by, or probably caused by research activity, or, if a device is involved, probably caused by, or associated with the device, AND
3. Harmful – caused harm to participants or others, or placed them at increased risk of harm (including physical, psychological, economic, or social harm).

Definition of reportable information:

1. New information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency.
2. Complaints that are unresolved by the research team, or that indicates increased or unexpected risks.
3. Unanticipated adverse device effect. New information about the effect on health or safety.

Adverse events:

Pulmonary, esophageal, chest wall, skin, vascular, cardiac/pericardial, and brachial plexus/neurologic toxicity will be scored by the CTCAE 4.0 criteria.

The following grade 3 or higher adverse events will be reported to the protocol director.
These will be reported as definitely, probably, or possibly related to treatment:

• **Grade 3-5 Cardiac Disorders**
- Pericardial effusion
- Pericarditis
- Restrictive cardiomyopathy

• **Grade 4-5 Gastrointestinal Disorders**
- Dysphagia
- Esophagitis

- Esophageal fistula
- Esophageal obstruction
- Esophageal perforation
- Esophageal stenosis
- Esophageal ulcer
- Esophageal hemorrhage

• **Grade 3-5 Injury, Poisoning, and Procedural Complications**
- Fracture (to be limited to rib fractures only)

• **Grade 3-5 Nervous System Disorders**
- Brachial plexopathy
- Recurrent laryngeal nerve palsy
- Myelitis

• **Respiratory, Thoracic, and Mediastinal Disorders, Grade 3-5, except as noted below**
- Atelectasis (grade 4-5 only)
- Bronchopulmonary hemorrhage
- Mediastinal hemorrhage
- Pleural hemorrhage
- Tracheal hemorrhage
- Bronchial fistula
- Pulmonary fistula
- Bronchopleural fistula
- Tracheal fistula
- Hypoxia (provided grade 3 is worse than baseline)
- Bronchial obstruction
- Tracheal obstruction
- Pleural effusion
- Pneumonitis
- Pulmonary fibrosis

• **Grade 3-5 Skin and Subcutaneous Disorders**
- Skin ulceration (thorax only)

• **Any Grade 5 adverse event attributed to treatment**

11.5 Stopping Rules

All outcome data (toxicity and efficacy) will be reviewed every 6 months by the Principal Investigators and key Co-Investigators. This study will be monitored by the DSMC. All potential adverse events will be reported to the thoracic disease

management group and the DSMC. The study will terminate when the target accrual is met and all data are analyzed.

11.6 Confidentiality

Study data will be maintained in protected patient binders. Only research personnel listed on this protocol will have access to this information. Only the patients unique IDN will be used. Specimens will be stored under the patient's IDN.

12. STATISTICAL CONSIDERATIONS: TYPE AND NUMBER OF EXPERIMENTAL SUBJECTS

12.1 Primary and Secondary Endpoints

Primary Endpoints:
Local tumor control of individually optimized lung tumor SABR.

Secondary Endpoints:

Toxicity of individually optimized lung tumor SABR

12.1.1 Feasibility of anatomically optimized AVB-coached breath-hold technique assisted by fast delivery using gated RapidArc with FFF in a subset of patients. Feasibility will be assessed based on:

(1) The proportion of patients able to reproduce an anatomically-optimized breath-hold with AVB-coaching during treatment.
(2) The reduction in treatment delivery time compared to gated free-breathing treatment.

12.1.2 Metastasis free and overall survival in patients treated with SABR.

12.2 Sample Size

12.2.1 Accrual Estimates

In 2009, 80 lung SABR procedures were performed at Stanford Hospital. We estimate based on the number of lung SABR procedures done a year that approximately 5-6 patients can reasonably expect to accrue per month with primary lung cancer or cancer metastatic to lung.

Accrual will occur over 48 months, at the rate of approximately 5-6 per month.

12.2.2 Sample Size Justification

This protocol targets three cohorts of patients: 1) patients with an initial diagnosis of limited primary NSCLCs (T1aN0M0, T1bN0M0, T2aN0M0, T2bN0M0, or T3N0M0) (i.e. no prior history of non-small cell lung cancer); 2) patients with a prior history of non-small cell lung cancer who have new limited primary NSCLC lesion(s); and 3) patients with more advanced lung cancer or lung metastases from a variety of different cancers. The three cohorts will be analyzed separately. A sample of size 82 for cohorts 1 and 3 was chosen in order to have 80% power to reject a rate of local control of 80%, if the true rate is 90%. Once cohorts 1 and 3 have enrolled 82 informative patients, the trial will be closed. Cohort 2 will likely have fewer than 82 patients and will have a larger margin of error. Approximately 86 subjects in cohorts 1 and 3 will be enrolled to allow for a 5% drop-out rate. Cohort 2 has been slower to accrue and we wish to conclude this phase of the study without waiting for full enrollment.

Specifically, proportions estimated on the basis of 82 subjects in each of cohorts 1 and 3 carry a margin of error (90% confidence interval) of 10 percentage points. If we observe a rate of local control of 90%, we will be able to exclude, with 95% confidence, a true rate less than 82%. Likewise, if the observed rate of grade 2+ toxicity is 30%, we will be able to exclude, with 95% confidence, a true rate of 39%; if we observe a rate of 15% grade 3+ toxicity (12/82), we will be able to exclude, with 95% confidence, a true rate of 23%. Precision for cohort 2 will be reduced.

In a collaborative effort, some patients will be accrued at Shantou, CUHK, and Hokkaido Universities in China and Japan. We expect no more than 10 patients to be enrolled at each of these sites. Accrual at these sites will not increase the total number of patients enrolled and will not change the statistical analysis.

12.3 Analysis populations

Analysis will be carried out in all patients who complete protocol procedures.

12.4 Plan of Analysis

Local control at 12 months will be estimated along with a one-sided lower 95% confidence bound to allow an informal assessment of the null hypothesis that the proportion is larger than 80%. Patients with distant progression before local failure will be censored one day after the last imaging study; patients who die before local control

will be censored at the time of death. These definitions are used for comparability. Cumulative incidence estimates for local failure and other failure type will also be presented.

Time to event data (local control, PFS, time to progression) will be evaluated using Kaplan-Meier estimates with 95% confidence intervals at multiples of 12 months based on Greenwood's formula with a log transform. Confidence intervals for median times to event, if relevant, will be constructed using the method of Brookmeyer and Crowley.

Biomarkers (e.g. cfDNA) will be summarized using medians and interquartile ranges; changes in biomarkers will be assessed using the Wilcoxon signed rank test. Correlation of biomarkers with local control and progression will be evaluated informally using a Wilcoxon rank sum test on patients with and without the event of interest. If feasible, these analyses will be supplemented by more formal analyses with the Cox model.

Proportions (e.g. proportion of patients with grade 4 or higher toxicity) will be estimated along with 95% exact confidence intervals. Patient clinical and demographic characteristics will be reported with the appropriate summary statistic (mean, range, proportion etc.). Adverse events will be tabulated by organ system and severity.

13. INVESTIGATOR RESOURCES

13.1 Qualifications

The study staff will include, but is not limited to, the Principal Investigators, Co-Investigators, research coordinators, research nurses, and any residents or fellows working with the physicians. Also, laboratory personnel in the Principal Investigators' laboratory will be involved in analyzing the plasma and tumor specimens collected from patients.

All study staff have completed the required training specific for their responsibilities in this study. Furthermore, each member of the research team from each institution will be given a thorough explanation of the protocol and their responsibilities, including helping with scheduling, procedures, follow-up, data entry, or analysis. All research investigators will be required to complete proper training through their institutional review boards.

NOTE: The study staff at Shantou, CUHK, and Hokkaido must receive approval from their own IRBs to conduct the research in this protocol. They will also receive training from the Principal Investigators and Co-Investigators. The data collected at these sites will be sent to Stanford for review and quality assurance. We will also be doing remote data review.

13.2 Conflict of interest

Dr. Billy Loo received speaking honoraria from Varian and GE Medical Systems.

14. References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010; 60: 277-300.
2. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995; 60: 615-622; discussion 622-613.
3. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. The International Registry of Lung Metastases. J Thorac Cardiovasc Surg 1997; 113: 37-49.
4. Timmerman RD, Bizekis CS, Pass HI et al. Local surgical, ablative, and radiation treatment of metastases. CA Cancer J Clin 2009; 59: 145-170.
5. Hadziahmetovic M, Loo BW, Timmerman RD et al. Stereotactic body radiation therapy (stereotactic ablative radiotherapy) for stage I non-small cell lung cancer--updates of radiobiology, techniques, and clinical outcomes. Discov Med 2010; 9: 411-417.
6. Crabtree TD, Denlinger CE, Meyers BF et al. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. J Thorac Cardiovasc Surg 2010; 140: 377-386.
7. Timmerman R, Paulus R, Galvin J et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010; 303: 1070-1076.
8. Rusthoven KE, Kavanagh BD, Burri SH et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. J Clin Oncol 2009; 27: 1579-1584.
9. Wulf J, Baier K, Mueller G, Flentje MP. Dose-response in stereotactic irradiation of lung tumors. Radiother Oncol 2005; 77: 83-87.

10. Onishi H, Shirato H, Nagata Y et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007; 2: S94-100.
11. Timmerman RD, Park C, Kavanagh BD. The North American experience with stereotactic body radiation therapy in non-small cell lung cancer. J Thorac Oncol 2007; 2: S101-112.
12. Le QT, Loo BW, Ho A et al. Results of a phase I dose-escalation study using single-fraction stereotactic radiotherapy for lung tumors. J Thorac Oncol 2006; 1: 802-809.
13. Brown JM, Diehn M, Loo BW, Jr. Stereotactic ablative radiotherapy should be combined with a hypoxic cell radiosensitizer. Int J Radiat Oncol Biol Phys 2010; 78: 323-327.
14. Xue X, Zhu YM, Woll PJ. Circulating DNA and lung cancer. Ann N Y Acad Sci 2006; 1075: 154-164.
15. Schwarzenbach H, Hoon DS, Pantel K. Cell-free nucleic acids as biomarkers in cancer patients. Nat Rev Cancer 2011; 11: 426-437.
16. Sozzi G, Conte D, Leon M et al. Quantification of free circulating DNA as a diagnostic marker in lung cancer. J Clin Oncol 2003; 21: 3902-3908.

APPENDICIES

Appendix I
Eligibility Checklist

A Participant Eligibility Checklist must be completed in its entirety for each subject prior to registration. The completed, signed, and dated checklist must be retained in the patient's study file and the study's Regulator Binder.

Study Name: **Phase II trial of individualized lung tumor stereotactic ablative radiotherapy (SABR)**

Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

Study Information: SRC Approved ☐ IRB Approved ☐ Contract signed ☐

Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation**
1. Limited primary lung tumors or metastatic lung tumors. Limited primary tumors are early-stage NSCLCs (T1aN0M0, T1bN0M0, T2aN0M0, T2bN0M0, or T3N0M0). Up to 4 lesions may be	☐	☐	**14.1.1.1**

included. For a single lesion the sum of three orthogonal diameters can be no more than 20 cm. For multiple lesions, no lesion can have a sum of orthogonal diameters greater than 15 cm.			
2. Histologic confirmation (strongly encouraged but not required when clinical suspicion of malignancy is high)	☐	☐	
3. Age >= 18 years old.	☐	☐	
4. History and physical performed within 12 weeks of registration.	☐	☐	
5. CT scan of thorax with or without contrast (with contrast is preferable) performed within 8 weeks of registration.*	☐	☐	
6. FDG PET scan performed within 8 weeks of registration.*	☐	☐	
7. Study-specific informed consent signed prior to study entry.	☐	☐	
Exclusion Criteria (From IRB approved protocol)			
1. Evidence of uncontrolled extrathoracic metastases.	☐	☐	
2. Contraindication to receiving radiotherapy.	☐	☐	
3. Pregnant or breastfeeding woman or woman of childbearing potential who is unwilling or unable to use acceptable method of birth control (hormonal or barrier method of birth control; abstinence) to avoid pregnancy for the duration of the study.	☐	☐	
4. Prior radiation therapy is allowed but there should not be overlap with the prior high dose regions unless approved by the protocol directors.	☐	☐	

*****CT and PET scans obtained at the time of simulation are acceptable. PET is not required if tumor is known to be
PET negative from prior scans, or for oligometastatic tumors of non-lung primary.
All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation
can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical
record review.

Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study.
This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	

Appendix II

EORTC QLQ-C30 and

EORTC QLQ-PAN26

[redacted]