Lung Volume Reduction for Severe Emphysema by Stereotactic Ablative Radiation Therapy

Study Protocol

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A Phase I Clinical Study of Lung Volume Reduction by Stereotactic Ablative Radiotherapy in the Treatment of Severe Emphysema

Emphysema

Chronic Obstructive Pulmonary Disease (COPD) is a major, worldwide public health problem. Consisting of emphysema, chronic bronchitis, and combinations of the two, COPD is the third most frequent cause of death in developed countries, and a major cause of morbidity, reduced quality of life, and costs to health care systems. Severe COPD is estimated to be present in 10.1% of the world's population (1). Even after smoking cessation, pulmonary dysfunction resulting from the inflammatory process of COPD unfortunately continues to progress, albeit at a slower rate.

Treatments for COPD are almost entirely palliative, consisting of inhaled bronchodilators, inhaled steroids, and sometimes systemic steroids as chronic therapy; and antibiotics with or without steroids for acute exacerbations. Once the forced expiratory volume in one second (FEV1, the most standardized measure of severity of COPD) falls below 30%, the mean two year survival in emphysema patients is only approximately 60%. The only non-surgical therapy which has been shown to have impact on this dismal survival in severe COPD is oxygen therapy for patients who are hypoxic.

The pathophysiology of COPD is complex. In emphysema, however, the major component of the pathophysiology, and thus the cause of much of the dyspnea associated with the disease, is *pulmonary hyperexpansion.* The elastin fibers in emphysematous lungs are progressively destroyed, resulting in progressive enlargement of air spaces and

thus of the entire lung itself. As the lungs expand, they force the diaphragm and accessory respiratory muscles out of their usual, optimized positions. The diaphragm is flattened and its muscle fibers shortened, and the other respiratory muscles are similarly able to function far less efficiently. The resulting increased work of breathing is central to emphysema patients' sensation of dyspnea. Additionally, loss of elastic tethering fibers that normally support the airways allows the small to medium sized airways of emphysema patients to collapse upon expiration, creating a vicious cycle in which exhalation -- normally a passive event -- requires additional respiratory muscle work to be achieved. In chronic bronchitis, the hyperexpansion may be somewhat less pronounced and less important in the generation of symptoms; an inflammatory component, causing relatively fixed narrowing of the airways and mucous overproduction, is more prominent.

Lung Volume Reduction Surgery

Since medical therapies offer only modest palliation and minimal hopes for improved survival to COPD patients, surgical therapies have been designed that may provide greater benefits in selected patients. Lung transplantation, for example, clearly improves survival and quality of life in patients with end stage COPD. This comes at substantial economic cost, however, as well as the at the cost of complications that may result from the complex surgery and from life-long immunosuppression. In addition, nearly all lung transplants will fail within 5 years as a result of progressive bronchiolotis obliterans, which we currently have no way to prevent or treat.

A second operation designed to treat severe COPD patients is **lung volume reduction surgery (LVRS)**. This operation, designed for patients with predominant emphysema rather than chronic bronchitis, is among the most carefully studied operations ever developed. The National EmphysemaTreatment Trial (NETT) randomized severe emphysema patients (in a CMS-sponsored national study) to bilateral lung volume reduction surgery via median sternotomy versus "best medical therapy" (2, 3). This

study found that outside of the most severely ill patients enrolled (in whom the risks of the surgery outweighed the benefits), 3 out of the 4 remaining 'non-high-risk' subgroups derived major improvements in pulmonary function and quality of life, and 1 of the 4 subgroups actually derived a survival benefit from the operation. On average, appropriately selected patients will have a 50% improvement in their FEV1 following the operation (4).

Lung volume reduction surgery is performed via either median sternotomy or bilateral thoracoscopy. The goal of the procedure is to remove areas of emphysematous lung in order to reduce hyperexpansion, thereby restoring the respiratory muscles closer to their normal, efficiently-functioning positions, as well as restoring the lung's "elastic recoil," thereby increasing expiratory airflow. The ideal patients, as established in multiple studies including the NETT trial, have severe emphysema (FEV1 less than 45% of predicted), are markedly hyperexpanded (residual volume greater than 150% of predicted, preferably even higher), and have "target zones" – that is, heterogeneous distribution of disease such that there are areas of lung that are more severely involved and can be targeted for resection and other areas that are less severely involved. By removal of the areas that are more severely involved, one can reduce lung volume without removing lung that is contributing substantially to gas exchange (4).

Despite the clear benefits of the operation, it is associated with an approximately 5% mortality rate. Furthermore, because of the complexity of the care of these significantly compromised patients following general anesthesia and chest surgery, it can currently be performed only in sites that are either lung transplant centers or are certified specifically for LVRS, thus limiting access to the procedure. For these and other reasons, the operation is not performed with nearly the frequency that one might expect given its carefully documented effectiveness.

As a result, a variety of devices and procedures have been designed to try to create a "non-surgical lung volume reduction" -- which might be able to provide the benefits of LVRS without engendering the same degree of risk. These devices have consisted for the

most part ofendobronchial valves designed to be placed into segmental airways to either completely block, or to create one-way flow, through the airways. The goal of these devices is to collapse the targeted segments of the lung. Unfortunately, although these approaches incur less morbidity than surgical LVRS, they are not nearly as successful as surgical LVRS in improving pulmonary function and reducing dyspnea. The several pilot studies which have been performed to evaluate these approaches have generally demonstrated marginally *statistically* significant improvements in quality of life and pulmonary function but clearly not *clinically* significant improvements (5, 6).

It is thought that the failure of endobronchial valves to create successful lung volume reduction is due to the presence of collateral ventilation between segments and lobes in emphysema patients. Pores are present which allow anatomic regions of the lung to exchange air even across fissures. Thus, even after occluding a segmental bronchus, that segment is likely to remain expanded as a result of collateral ventilation from adjacent segment and lobes. This would render any attempt at endobronchial lung volume reduction to fail. Because of the failure of the non-surgical modes of volume reduction currently under evaluation, this remains an active area of investigation by a number of universities and commercial concerns.

Stereotactic Ablative Radiotherapy

Stereotactic Ablative Radiotherapy (SABR), also called stereotactic body radiation therapy (SBRT), is a relatively recent advance in radiotherapy which allows high doses of radiation to be transmitted to focused areas (typically malignancies), allowing higher rates of tumoricidal activity, generally lower complications, and greater convenience for patients since it can be delivered in 1 to just a few sessions. As the radiation is administered from multiple directions according to stereotactic planning, high doses can be delivered to the tissues with rapid fall-off to relatively low doses in even nearby, surrounding normal tissues. This technique was initially applied to brain tumors– an application which over the years has met with great success. More recently, it has been

applied with substantial success and is gaining increasing acceptance as a primary mode of therapy for stage I lung malignancies, and malignancies in multiple other body areas.

In the lung, the rate of pneumonitis resulting from SABR is far lower than the rates incurred by conventional external beam radiotherapy. In conventional external beam radiotherapy reported pneumonitis rates range from 13-37% (7), depending on dose and field size. Reported rates of symptomatic pneumonitis after lung SABR are significantly lower and generally are ~5% (8). SABR does, however, typically leave a scar in the area of lung that has been treated (9). Importantly, there appears to be contraction of surrounding lung parenchyma into this scar resulting in an effect that is essentially a "lung volume reduction." One often sees clear loss of lung volume following any form of lung radiotherapy. With SABR, this "volume reduction" is achieved with a far lower risk of morbidity – in particular, less risk of pneumonitis.

Stereotactic Ablative Radiotherapy for Emphysema

We hypothesize that we can create a minimally invasive form of LVRS by applying SABR to target areas of the lung in severe emphysema patients, creating limited scarring and retraction of tissue and thus "volume reduction". We believe that by reducing the volume of emphysematous lung with the precise target localization made possible by image-guided SABR, that we will be able to duplicate the benefits of surgical lung volume reduction with far less risk. We believe that this may represent a major advance in the therapy of emphysema – a highly prevalent disease. It may provide not only palliation but also increased survival, as does surgical lung volume reduction, in carefully selected patients.

LVRS via SABR (or **Stereotactic Ablatic Volume Reduction – SAVR**) should avoid the problem of collateral ventilation, described above, which appears to underlie the failure of other attempts at minimally invasive forms of LVRS. Like surgical LVRS, SAVR will actually ablate areas of lung, resulting in their essential disappearance. Surgical LVRS allows actual surgical excision of these areas of lung; SAVR would

shrink these areas of lung into small scars which would take up far less space within the chest than the untreated lung. We hope that this will engender all the benefits of surgical lung volume reduction.

Although surgical LVRS is often carried as a bilateral procedure (upon both lungs) under a single anesthetic, many centers perform the operation unilaterally, reserving the opposite side to be operated upon only subsequently, if indicated. Given that this unilateral approach has also been demonstrated to result in major improvements in pulmonary function and quality of life, we are electing to carry out unilateral SAVR for the first 5 patients in this protocol, extending this to bilateral SAVR in the last 5 patients if there are no major adverse events through the initial 5..

Preliminary Data

Fibrosis in lung tissue irradiated to a high dose is a well-known phenomenon after conventional radiotherapy. More recently, studies have characterized this phenomenon more systematically in patients treated with SABR (9, 10). These fibrotic changes develop over time in 99% of patients treated with SABR for lung tumors, 73% within one year (10). Of note, this occurs despite the usual attempt to *minimize* the volume of lung tissue irradiated in the context of treating early stage lung cancer. A greater effect can be anticipated if lung tissue is *deliberately targeted* for ablation, as the development of fibrosis is known to be related to the irradiated volume.

Actual intentional volume reduction as a result of a fibrotic response to SABR, and concomitant expansion of the remaining portions of the lung, has not been previously reported to our knowledge. We have, however, observed this phenomenon in several patients in our own experience at Stanford. Figure 1 shows an example of a patient treated with SABR for an early stage lung cancer of the right upper lobe. After treatment, the right lung apex was replaced with fibrosis where the tumor had been located, and the change in the position of the major fissure clearly reflects both volume loss in the right upper lobe and volume expansion of the right lower lobe – precisely what is achieved by

surgical LVRS. Again, this effect was not the intent of the treatment, which in this and all other patients treated to date, was focused on the tumor. If, however, volume reduction by shrinkage of lung tissue became the goal of the SABR, this effect could presumably be optimized by appropriate targeting of lung tissue.

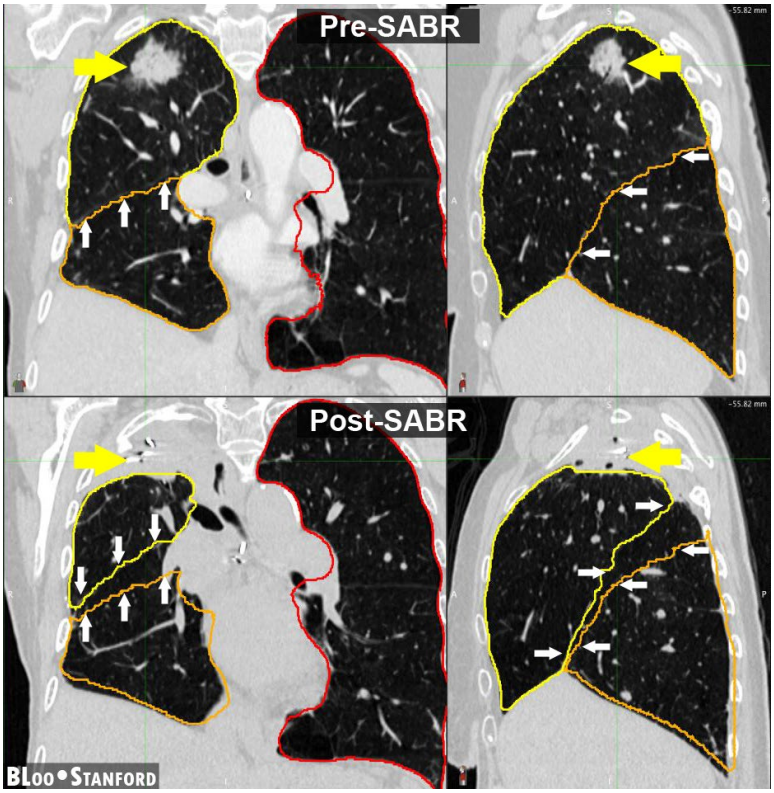

Figure 1. Lung volume reduction after SABR for a right upper lobe tumor. Coronal and sagittal sections demonstrate that following SABR, there is fibrosis of the right lung apex where the radiation has been delivered to tumor (large yellow arrow), and volume loss within the right upper lobe, indicated by craniad deviation of the major fissure, with corresponding expansion of the right lower lobe (small white arrows). Note also that the mediastinum is deviated to the side of the treatment.

Intriguingly, in the 1970's a pilot study used now antiquated radiation therapy technologies to attempt to induce lung fibrosis in emphysematous lung regions in order to improve overall lung function (11). The treatment was found to be safe and achieved subjective improvement in dyspnea in all ten patients, but it did not achieve clear,

objective improvements in lung volumes. It stands to reason that precise radiotherapy to specifically targeted lung volumes should achieve more impressive results.

Study Design

We propose a 10 patient, phase I study to determine safety and feasibility of SAVR.. All patients will each be treated with approximately the same SABR dose, unilaterally (with minor modifications based on the precise anatomy of the emphysematous changes in their parenchyma). The primary outcome will be the occurrence of grade 3 or higher adverse events, as listed below. Secondary outcome measures, in order to determine initial effectiveness of the procedure, will include post-procedure pulmonary function, exercise capacity, and quality of life.

Study subjects may be candidates for surgical LVRS, and all subjects who are good candidates for surgical LVRS will be offered the surgical procedure as well as entry into the study. We therefore expect that most subjects enrolled will be individuals who are not optimal candidates for surgical LVRS.

Inclusion Criteria

These criteria are modified from those established by the NETT and other single-institution studies establishing the criteria for relative safety and effectiveness of surgical LVRS.

Pulmonary Function

Severe COPD with severe reduction in quality of life due to dyspnea

Moderate to Severe emphysematous destruction of lung parenchyma on chest CT

FEV1 < 45% predicted and >18% predicted

FEV1/FVC < .7

DLCO > 18% predicted

Residual Volume > 160% predicted (by plethysmography)

Arterial Blood Gas

paO2>40 on room air at rest

paCO2<55

General

Successful completion of 16 sessions of pulmonary rehabilitation

Exclusion Criteria

Left ventricular ejection fraction below 40%

Predominate chronic bronchitis (none or mild emphysematous destruction of lung on chest CT)

Pulmonary function tests / lung volumes that do not meet above criteria.

Active coronary ischemia (stress test required if clinical symptoms).

Inability to complete 16 sessions of pulmonary rehabilitation.

Recent (less than 3 months) hospitalization with or without the COPD exacerbation.

Recent (less than 3 months) pulse dose steroids usage.

Pregnancy. Presence of lung cancer.

Procedures: Initial Evaluation and Pre-procedural preparation

1. **Initial evaluation –** Patients will be evaluated by the PI and study coordinator in the thoracic surgery clinic of the PI. Evaluation will include the standard evaluation for surgical LVRS, which includes history and physical examination, and the CT chest as well as PFT studies required to evaluate for fulfillment of the inclusion/exclusion criteria.

   The option of surgical LVRS, if the patient is a candidate for surgical LVRS, will be discussed, as well as the option of entering this study of LVRS by SABR.

Studies to be completed to determine suitability for protocol enrollment:

CT Chest

Pulmonary function testing including spirometry, DLCO, plethysmographic lung volumes

Arterial Blood Gas (room air, at rest)

Patients who meet inclusion/exclusion criteria will sign informed consent to enroll in the study.

2. **Pre-procedural preparation -** All patients who are enrolled in the study must, in addition to the above studies, undergo the following prior to SABR therapy:
    a. 16 sessions of pulmonary rehabilitation
    b. 6 minute walk test
    c. SF36 quality of life assessment and St George's questionnaire.
    d. . EKG test

Procedures*: SABR Administration and Radiation Treatment Planning*

1. Simulation

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

2. Treatment planning

The PI (surgeon) and one of the co-PIs (radiation oncologist) will together contour the area of lung to be targeted. This will consist of the region of greatest parenchymal destruction by emphysema, which could be as large as an entire lobe if normal tissue constraints are met, and will be

designated as the clinical target volume (CTV). Breathing-induced target motion will be assessed using the 4-D CT data and managed by respiratory gating or motion-inclusive technique, and the internal target volume (ITV) will be designed accordingly. There will be no additional set-up margin and therefore the planning target volume (PTV) will be identical to the ITV.

Treatment will be delivered using 6 MV photons on the Trilogy or TrueBeam platforms (Varian Medical Systems, Palo Alto, CA), using daily kilovoltage (kV) x-ray portal imaging and cone-beam CT for anatomy-based matching. The analytical anisotropic algorithm (AAA) will be used for dose calculations (or Acuros XB when available), and treatments will be delivered by either dynamic conformal arc therapy (DCART) or volumetric modulated arc therapy (VMAT, RapidArc, Varian).

3. SABR Treatment Delivery:

The prescribed dose will be 45 Gy in three fractions of 15 Gy, on each side that is treated. In the first 5 patients we will treat only 1 lung (unilateral SAVR); if there are no major treatment-related adverse events in the first 5 patients, we will plan bilateral LVRS, if anatomically appropriate, in the last 5 patients.

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 V100%RX = 95%). The global maximum dose point should be within the PTV and ideally within the CTV.

We will exclude prescription-dose planning target volumes (PTV) that overlap with the proximal bronchial tree (carina to lobar bronchi) and mediastinal structures (heart, esophagus, aorta, SVC, main pulmonary artery).

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

Ratio of Prescription Isodose Volume to the PTV Volume		**Maximum Dose @ 2 cm from PTV (in % of dose prescribed)**	
Ideal	**Required**	**Ideal**	**Required**
<1.2	<1.5	<60	<75

Critical organ dose constraints

The following tables list dose constraints to critical structures. Exceeding these dose limits by more than 5% constitutes an unacceptable protocol deviation.

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-PTV (i.e. non-targeted lung)	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 <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 (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 limitsmay be exceeded for an otherwise excellent plan. This will not be considered a violation.

All study data will be stored securely in a Stanford-hosted red cap database.

Post-SABR Follow-up

Patients will be followed for 1.5 years following the experimental treatment, according to the following follow-up schedule. Attention at each visit will be directed to the presence of clinical signs or radiographic changes suggesting pneumonitis or other adverse events. All adverse events will be recorded and scored:

2 months CXR and office visit
6 months CT chest, office visit, PFTs, SF 36 QOL assessment, 6 minute walk
12 months CT chest, office visit, PFTs
18 months CT chest, office visit, PFTs, SF 36 QOL assessment, 6 minute walk

Data Analysis

PFTs (FEV1, DLCO, RV) will be compared preop vs. each postop time point

6 minute walk test will be compared preop vs. each postop time point

SF36 and Borg dyspnea scores will be compared preop vs. each postop time point

Evaluation for Adverse Events

Toxicity will be scored according to the NCI CTCAE v4.0.

Serious adverse events (SAE's) will be reported to the Stanford PI and to the IRB, and DSMB as per the Cancer Clinical Trials Office Standard Operating Procedure for SAE reporting.

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

Data Safety Monitoring Board (DSMB)

This study's data analysis will be performed by Dr. Max Diehn, who has no conflicts of interest.

We have constituted a DSMB consisting of Dr. Leah Backhus (thoracic surgery), Dr. Arthur Sung (pulmonary medicine), and Dr. Daniel Chang (radiation oncology). They will review the collected clinical data after 3 patients have been treated and followed for 6 months and determine if the study should be continued to completion. An adverse event definitely or probably related to the treatment which causes death (within the first 3 patients treated) would dictate termination of the study. The following findings would dictate termination of the study at the scheduled interim DSMB review:

-3 treatment-related grade 3 or higher adverse events

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