Stereotactic Ablative Radiotherapy of Refractory Ventricular Tachycardia – a Phase I/II Study

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INDEX

PROTOCOL SYNOPOSIS:

CONCEPT/RATIONALE:

Sudden cardiac death accounts for more than 326,000 deaths per year in the US alone, and a significant portion of these are attributable to ventricular arrhythmia subsequent to ischemic (ICM) or non-ischemic cardiomyopathy (NICM). Even with current gold-standard therapies, a large number of patients have uncontrolled arrhythmia leading to either death or poor quality of life due to recurrent implantable cardioverter defibrillator (ICD therapies) shock rescue.

Stereotactic ablative radiotherapy (SABR) is routinely used in radiation oncology to accurately ablate small moving targets in single session treatments with minimal toxicity. There is preliminary data in both animal studies and clinical case reports of control of VT in otherwise refractory patients following a 30-min single session stereotactic ablative radiotherapy.

This protocol will offer compassionate use/palliative therapy for patients that have failed all other available therapies. During this initial study, data will be gathered on efficacy and toxicity to guide future multi-institutional studies. This is a highly collaborative effort between radiation oncology, radiology and cardiology/cardiac electrophysiology. If successful, this non-invasive approach to treat ventricular arrhythmias has the potential to significantly impact the quality of life and mortality risk of a large group of patients who at this time have few viable treatment options.

PRIMARY OBJECTIVE (S):

(1) Phase Ib portion: To determine maximal tolerated dose (MTD) for stereotactic ablative radiotherapy of targets in the cardiac myocardium
(2) Phase IIa portion: To make a preliminary assessment of the efficacy of stereotactic ablative radiotherapy technique for the control of ventricular arrhythmia

SECONDARY OBJECTIVE (S):

(1) To determine impact on overall cardiac function (ejection fraction)
(2) To determine impact on quality of life
(3) To determine impact on overall survival
(4) To assess treatment-related toxicity by serum markers, imaging, and histology

PRIMARY ENDPOINT (S):

(1) Phase Ib portion: Achievement of maximal tolerated dose of SABR
(2) Phase IIa portion: To estimate the ICD shock free survival rate at the MTD of SABR

SECONDARY ENDPOINT (S):

(1) Salvage definitive anti-arrhythmia therapy (cardiac transplant)
(2) Return of ventricular tachycardia requiring defibrillation, intravenous drug therapy or readmission to hospital.
(3) Ventricular tachycardia burden as measured by number of ICD shocks in the periods of 3,6 and 12 months pre and post the SABR procedure
(4) Decline of LV ejection fraction by more than 5% on two consecutive echocardiograms
(5) Persistent increase in baseline supplemental oxygen requirement by 1L for a duration of >3 months
(6) Use of steroids for radiotherapy related indications

(7) Overall survival
(8) QOL Questionnaire (SF-36)

STUDY DESIGN:
Single arm, phase Ib/2a dose escalation study with an expansion cohort to determine the maximal tolerated dose (MTD) for stereotactic ablative radiotherapy of targets in the cardiac myocardium and to make a preliminary assessment of the efficacy of the treatment. The dose escalation will be guided by Time-to-Event Continual Reassessment Method (TITE-CRM) to ensure more patients will be spared dose limiting toxicities and more patients will be entered on the dose level that will be chosen as minimal dose of maximal effect. This design also allows for continual accrual of patients when delayed adverse events may be observed.

NUMBER OF PATIENTS:
30

ELIGIBILITY CRITERIA:
- Documented sustained ventricular arrhythmias refractory to or not a suitable candidate for catheter based RFA ablative therapy
- Documented sustained ventricular arrhythmias refractory to or not a suitable candidate for cardiac sympathetic denervation therapy
- Documented ventricular arrhythmias refractory to or not a suitable candidate for cardiac transplantation
- Documented sustained ventricular arrhythmias refractory to or not a suitable candidate for additional medical management
- ICD in place with documented episodes recurrent VT despite best clinical management previous refusal of ICD with recurrent sustained ventricular arrhythmias
- If ischemic cardiomyopathy, myocardial infarction occurred more than one month prior to enrollment
- No history of prior radiotherapy to the chest
- Prescribed dose must be deliverable using SABR technique
- Age ≥ 18 years
- Karnofsky Performance Status (KPS) $\geq$ 70
- If a woman is of childbearing potential, a negative serum pregnancy test must be documented. Women of childbearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; or abstinence) for at least 4 weeks after study treatment.
- Ability to understand and willingness to sign a written informed consent

INTERVENTION AND MODE OF DELIVERY:
Intervention will be delivered on a clinical device radiotherapy system capable of stereotactic radiotherapy to the chest, with on-board image guided radiotherapy capabilities, respiratory motion management, and Intensity Modulated Radiotherapy Treatment (IMRT) planning.

DURATION OF INTERVENTION AND EVALUATION:
Study treatment will be single fraction stereotactic ablative radiotherapy (SABR) with routine clinical follow up for five years or until heart transplant or death.

STATISTICAL METHODS:

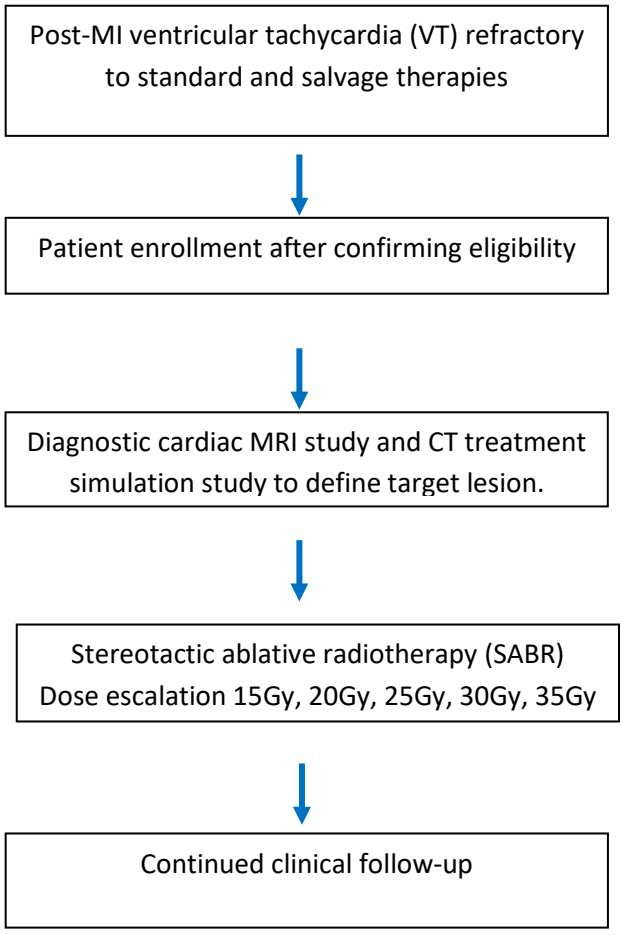
SAMPLE SIZE JUSTIFICATION:
Phase Ib portion: Dose escalation will be based on Time-to-Event Continual Reassessment Method (TITE-CRM). A sample size of 22 patients will be used. Monte Carlo simulations show that the proposed sample size has acceptable probability of correctly selecting a dose with acceptable toxicity and enough patients treated about the target dose for characterization of the efficacy endpoints, while being feasible for completion within 25 months.

Phase IIa portion: Approximately 8 additional patients will be enrolled at the MTD. Based on the simulation results for Phase 1b, a total of 16-20 patients (8-12 patients in the dose escalation cohort and 8 in the expansion cohort) will be used to assess efficacy. Literatures suggest 6-month ICD shock free survival rate is about 50%. Assuming the proposed SABR treatment will yield 6-month ICD shock free survival rate of 80%, a sample size of 16 patients achieves 80% power to detect a 30% difference in 6-month ICD shock free survival, using a one-sided one-sample exact Binomial test, at a 0.10 significance level.

FUNDING, REGULATORY, AND FEASIBILITY ISSUES:
UCLA Department of Radiation Oncology has the capability, equipment, and expertise to perform highly accurate stereotactic radiotherapy. Diagnostic cardiac MRI with and without contrast will be used for evaluation and treatment planning purposes. Electrophysiologic study data may be incorporated into treatment planning. Clinical and radiographic follow-up will be performed per standard of care with blood samples and questionnaires (SF-36) issued per study protocol. Study associated costs outside of standard of care will be covered by the Department of Radiation Oncology.

PATIENT ACCEPTABILITY/ETHICS AND CONSENT ISSUES:
Only patients able to give informed consent will be eligible for the study

SCHEMA


Post-MI ventricular tachycardia (VT) refractory to standard and salvage therapies
Patient enrollment after confirming eligibility
Diagnostic cardiac MRI study and CT treatment simulation study to define target lesion.
Stereotactic ablative radiotherapy (SABR)
Dose escalation 15Gy, 20Gy, 25Gy, 30Gy, 35Gy
Continued clinical follow-up

1.0 OBJECTIVES

1.1 Primary objectives

1.1.1 To determine the maximal tolerated dose of SABR to cardiac targets and whether SABR to the region of origin of the clinical ventricular arrhythmia decreases the risk of recurrent ICD therapies or sustained ventricular arrhythmias in otherwise refractory patients.

1.2 Secondary objectives

1.2.1 To determine impact on overall cardiac fitness
1.2.2 To determine impact on quality of life
1.2.3 To determine impact on overall survival
1.2.4 To assess treatment-related toxicity by serum markers, imaging, and histology

2.0 BACKGROUND

Sudden cardiac death (SCD) is a significant public health hazard, accounting for more than 326,000 deaths per year in the US alone[1]. This is a larger toll than deaths from lung, colon, breast and prostate cancers combined. In part, this bleak statistic is due to resuscitation being successful in only some 10% of cases [2]. Even the routine use of implantable cardioverter-defibrillators (ICDs) to rescue patients from these arrhythmias in the context of either primary or secondary prevention have been less than ideal, as elderly patients may actually exhibit increased mortality even when these devices function appropriately[3]. Thus, attention has been focused mainly on preventing the malignant arrhythmias that contribute to SCD. Estimates vary, but some 22% of SCD patient initially present with VT, and in select populations, up to 83% of SCDs can be attributed to ventricular arrhythmia [4, 5]. In the majority of cases, the life-threatening arrhythmias arise from slowly conducting scar related circuits that result from devitalized cardiac tissues following a myocardial infarction or other insult. Conventional therapies for ventricular arrhythmia have significant drawbacks with respect to impact on quality of life, invasiveness, and efficacy. For example, gold standard front-line therapy for those who fail anti-arrhythmic drug therapy consists of endocardial catheter ablation. However, in large multi-center trials the efficacy of catheter based ablation is around 50% at 12 months [6, 7]. In part, this is explained by substrate mapping issues, including complex arrhythmias with multiple potential reentry circuits, unstable VTs due to hemodynamic intolerance, and reentry paths deep to the endocardium which limit the efficacy of ablation. When endocardial ablation fails, pre-existing limited cardiovascular fitness of these patients and procedural expertise limited to relatively few specialized centers make the more complex subxiphoid percutaneous epicardial approaches available only to a minority of patients.

Should these procedures fail to control recurrent VT's, salvage procedures are available but again with significant limitations. For example, cardiac transplantation has traditionally been the salvage therapy of choice. However, the both the functional demands this treatment places on patients and the limited number of available donor organs have made this a relatively uncommon salvage treatment. More recently, surgical resection of the bilateral stellate ganglion pioneered at UCLA has shown improved success, with control of some 50% of patients refractory to medical and ablation therapies [8, 9]. Despite its promise, the technical demands of this technique have limited its applications to a few number of academic centers, and has thus limited its impact to-date. Given the prevalence of VT in patients with structural heart disease and the modest at best success of current interventional therapies, a large number of patients

are left without effective therapy. These patients are usually maintained on defibrillators that are life-saving, but with unpredictable electrical shocks which significantly detract from their quality of life, and in some populations' length of life [3].

Within the field of radiation oncology, there is a large body of experience and techniques for very accurate delivery of radiation to very small targets – stereotactic ablative radiotherapy (SABR). Within the cranium, for example, targets that are millimeters in diameter are verifiably treated with high doses of radiation with sub-millimeter accuracy. This has been routine practice now for many decades. Outside of the cranium, the periodic motions of respiration and cardiac contractions have made this targeting more challenging. Even then, motion management systems developed recently are able to reduce the error of delivery of high dose radiation delivery to below 5-millimeters. These consist of either fixed abdominal compression to minimize diaphragm travel, or algorithms to track and predict target location based on the periodicity of the respiratory cycle. Both these techniques are now in routine clinical use to allow extra-cranial stereotactic ablative radiotherapy (SABR). Within the chest, this is most commonly directed against early stage lung malignancies as well as oligometastatic lesions. Ablation of targets with SABR techniques have the advantage that targets are treated under direct visualization, the treatment is non-invasive, can be completed in a single session, and patients return home immediately after. The ability to non-invasively and accurately ablate small targets within the body offers a multitude of therapeutic opportunities outside of oncology. This project will pioneer SABR techniques specifically for anti-arrhythmic indications.

Early large animal studies have shown that a sufficiently high dose of radiation can be delivered safely to a targeted area of the ventricular myocardium, and that this treatment causes a homogenous scarring that suppresses local action potentials [10-12]. Long-term clinical and histopathological follow-up in these animal studies showed no significant toxicity outside the target region. In humans, there is a significant experience of the left ventricle receiving these high radiation doses incidentally, in the form inevitable dose spillage from SABR treatments for centrally located early stage lung cancers [13]. Regions of the heart exposed to a single dose of radiation >20 Gy begin to show metabolic changes on follow up PET scans at 6 months, but this does not correlate with any compromise of the cardiac function[14]. Indeed, the toxicity profile of SABR specifically directed against post-MI and non-ischemic lesions that are most likely substrates for slow conduction and VT is likely to be even superior to this, as these sections of the myocardium are already scarred from previous insult. With regard to efficacy, there are thus far only two independent case reports of first-in-man studies using the existing clinical linear accelerators systems on a compassionate use basis showing decreased VTs after targeted radiotherapy, and absence of treatment associated toxicity [15, 16]. In contrast animal studies, where electrophysiologic changes were seen months later, control of VTs in these two patients were noted starting some 48hrs from completion of treatment [15, 16].

3.0 PATIENT SELECTION

3.1 Conditions for patient eligibility

3.1.1 Documented ventricular arrhythmias refractory to or not a suitable candidate for catheter based RFA ablative therapy
3.1.2 Documented ventricular arrhythmias refractory to or not a suitable candidate for cardiac sympathetic denervation
3.1.3 Documented ventricular arrhythmias refractory to or not a suitable candidate for cardiac transplantation
3.1.4 Documented ventricular arrhythmias refractory to or not a suitable candidate for additional medical management
5. ICD in place with documented episodes recurrent VT despite best clinical management or prior refusal of ICD and recurrent sustained VT
6. If ischemic cardiomyopathy, myocardial infarction occurred more than one month prior to enrollment
7. No history of prior radiotherapy to the chest
3.1.7 Must be safely treatable with SRS
3.1.8 Age ≥ 18 years
3.1.9 Karnofsky Performance Status ≥70
3.1.10 if a woman is of childbearing potential, a negative serum pregnancy test must be documented. Women of childbearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; or abstinence) for at least 4 weeks following the study treatment.
3.1.11 Ability to understand and willingness to sign a written informed consent

3.2 Conditions for patient ineligibility

3.2.1 Patients who have previously received therapeutic radiation therapy to the chest
3.2.2 Patients who are eligible for standard of care salvage therapies
3.2.3 Patients with genetic conditions or co-morbidities making them ineligible for radiotherapy
3.2.4 Patients with concurrent arrhythmias outside the left ventricle
3.2.5 Pregnant women, or women of childbearing potential who are sexually active and not willing/able to use medically acceptable forms of contraception for the entire study period and for up to 4 weeks after the study treatment.
3.2.6 Refusal to sign the informed consent
3.2.7 Patients who are participating in a concurrent clinical trial

4.0 REGISTRATION PROCEDURES

4.1 General guidelines

Patients seen at UCLA as new or follow up patient with VT refractory to standard frontline and salvage therapies will be informed of this clinical trial if eligible. The decision to participate will be voluntary. Eligible patients who decides not to participate will continue to be offered standard therapies.

4.2 Registration Process

Informed consent form will be given to the patient for review. Consent will be obtained after a clear and thorough discussion between the patient and the study investigator in clinic. To register a patient, the research coordinator will obtain or complete: (1) Documentation of refractory ventricular tachycardia (VT;); (2) baseline LV ejection fraction within last 30 days; (3) List of previously failed procedures; (4) List of previously failed medications; (5) signed informed consent form; (6) signed HIPAA authorization form.

Upon confirmation of eligibility and enrollment in the study, the following will be obtained: (1) diagnostic cardiac MRI for radiation therapy planning, (2) CT-simulation, (3) routine cardiac panel blood samples (if not done within the previous 14 days) and research blood samples (50 ml), (4) Cardiac quality of life questionnaire (SF-36).

5.0 TREATMENT PLAN

5.1 Radiation Simulation and Planning

Enrolled patients, after confirmation of eligibility, will undergo radiation simulation and treatment planning. A thoracic alpha cradle will be used. This will be fused with diagnostic cardiac MRI with delayed enhancement sequences to identify the regions of scar potentially contributing to the clinical VT. This will also be fused with electro-anatomical mapping of previous electrophysiology 3-D mapping data if available.

The responsible study investigator(s), will delineate the regions of delayed enhancement visible on MRI as gross tumor volume (GTV). Areas outside the MRI scar identified by electrophysiology as harboring additional potential areas of critical to the clinical VT will be included in this volume. No expansion for clinical treatment volume will be used. Without respiratory gating, an internal target volume (ITV) expansion will be used. Planning target volume (PTV) expansion will consist of 6mm superior-inferior, with 6mm circumferential. Dose will be prescribed to the 70-80% isodose line to meet tolerance. PTV prescription dose will begin at 15Gy x 1, and increase in stepwise 3 by 3 fashion to 20Gy, 25Gy, 30Gy, and 35Gy per protocol safety parameters.

Delineation of normal structures including spinal cord, esophagus, heart, great vessels, trachea and large bronchus, rib, skin, stomach, and bilateral lungs will be performed. The radiation physicist will optimize the radiation therapy treatment plan and the responsible study investigator(s) will review it prior to approval for treatment. Dose volume histograms (DVH), and normal tissue constraint parameters specified below will be used to judge the quality of the plan and optimize doses to the GTV/PTV as well as maximally sparing of organs at risk (OARs). The dose and volume of the heart will be recorded.

Treatment will be delivered in a single session treatment lasting 30-45 minutes in the Department of Radiation Oncology. Patient will be accompanied by an electrophysiology attending to ensure patient safety. The treatment area will have prearranged ACLS supplies in place prior to patient arrival.

5.2 Objects at Risk (OAR) Dose Constraints

The dose constraints below for OARs will be used to assess the dosimetry for the plan. Doses that exceed the constraints below can be delivered if study investigators agree that the deviation is acceptable and unlikely to cause excessive morbidity.

Serial Tissue	**Volume (cc)**	**Volume Max (Gy)**	**Max Point Dose (Gy)**	**Endpoint (≥Grade 3)**
Spinal Cord	<0.35 cc <1.2 cc	10 Gy 7 Gy	14Gy	myelitis
Esophagus	<5 cc	11.9 Gy	15.4 Gy	stenosis/fistula
Brachial Plexus	<3 cc	14 Gy	17.5 Gy	neuropathy
Great Vessels	<10 cc	31 Gy	37 Gy	aneurysm

Trachea and Large Bronchus	<4 cc	10.5 Gy	20.2 Gy	stenosis/fistula
Rib	<1 cc	22 Gy	30 Gy	pain or fracture
Skin	<10 cc	23 Gy	26 Gy	ulceration
Stomach	<10 cc	11.2 Gy	12.4 Gy	Ulceration/fistula
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**		**Endpoint (≥Grade 3)**
Lung (Right & Left)	1500 cc	7 Gy		Basic Lung Function
Lung (Right & Left)	1000 cc	7.4 Gy		Pneumonitis

5.3 Patient follow-up after treatment
Patients will be followed clinically after treatment, including routine evaluation of recordings of VT on the calendar day post-treatment, 1 week (+/- 7 days), 1 month (+/- 7 days), 3 months, 6 months, 9 months, 12 months, 15 months, 18 months and 21 months post treatment (+/- 2 weeks) and every six months thereafter (+/- 2 weeks) until 60 months post-treatment or until death or until heart transplant.

Routine cardiac panel blood samples and research blood samples (50 ml) will be collected on the calendar day following treatment and 1 week after treatment (+/- 7 days), 1 month post treatment (+/- 7 days), and at 3 months post-treatment (+/- 2 weeks) and 12 months post-treatment (+/- 2 weeks).

Patients will fill out questionnaire (SF-36) at each follow up visit.

Patients will continue any other routine follow up visits and monitoring with their electrophysiologist as is routine for patients with ICDs and VT.

5.4 Criteria for removal from study
5.4.1 The patient withdraws.
5.4.2 The investigator may withdraw a patient from the study for one or more of the following reasons: failure of the patient to follow instructions of the protocol study staff, the investigator decides that continuing participation could be harmful to the patient, the patient is not tolerating treatment times/patient discomfort, the patient needs treatment not allowed in the study, the study is cancelled, other administrative reasons or unanticipated circumstances.

6.0 PHARMACEUTICAL INFORMATION
6.1 Investigational Agent or Device
Device

6.2 Availability
Not applicable.

6.3 Agent Ordering
Not applicable.

6.4 Agent Accountability
Not applicable.

7.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS
Toxicity assessment will be performed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0 for early (≤ 3 months), and late (> 3 months) radiation toxicity.

7.1 Treatment Toxicities
7.1.1 Constitutional symptoms
Constitutional symptoms that may be attributed to radiation therapy may include loss of appetite, nausea, and vomiting. Patients will be seen while they are receiving radiation therapy per standard of care. Counseling and medications may be prescribed to alleviate these symptoms while the patient is on treatment. It is expected that symptoms will improve and resolve 2-4 days after completion of therapy.

7.1.2 Radiation esophagitis
Radiation esophagitis is due to radiation-induced inflammation of the esophagus, and may appear starting several days after treatment. Patient will be seen on a weekly basis while they are receiving radiation therapy per standard of care. Counseling and medications may be prescribed to alleviate these symptoms while the patient is on treatment. It is expected that that symptoms will improve and resolve 2-4 days after completion of therapy.

7.1.3 Radiation pneumonitis
Presenting symptoms of radiation pneumonitis are very similar to acute bacterial pneumonia. Patients present with fatigue, fever, shortness of breath, nonproductive cough, and pulmonary infiltrate on chest-x-ray or CT scan. On imaging, radiation-induced infiltrate are geometric in shape and conform to the high-dose regions that have been irradiated. The expected time-frame for radiation pneumonitis is 4 weeks to 12 weeks after completing radiation therapy to the thorax. Subjects will be informed of this risk, and counseled to call the principal investigator immediately. Management of radiation pneumonitis is very different from bacterial pneumonia, and may require a long slow-taper of high dose steroid therapy.

7.1.4 Skin reaction
Unintended skin reaction due to radiation therapy to the chest is now an uncommon side effect. However, if the target is close to the anterior chest wall, skin reaction may occur several days after the end of radiation therapy. Appropriate skin care and topical medications will be given to the patient when there are signs of skin reaction. It is expected to be self-limiting, and improve 1 week after the end of therapy.

7.1.5 Radiation pericarditis and fibrosis
Radiation therapy close to the pericardium may cause inflammation of the lining of the heart, and radiation-induced pericarditis. Fluid-accumulation in the pericardium may be a consequence. Symptoms can be similar to radiation pneumonitis: shortness of breath, fever, and dry cough. Signs on CT scan and clinical exam are keys to its expedient diagnosis. Since this toxicity occurs generally after radiation therapy between 4 weeks to 12 weeks, close follow-up after treatment is essential. Subjects will be informed of the risk, and counseled to call the principal investigator

immediately. Management includes watchful waiting, medication, as well as surgical option depending on timing and severity of the complication.

7.1.6 Radiation pulmonary fibrosis

Radiation pulmonary fibrosis is a potential late-side effect of radiation therapy to the thorax. Its severity may or may not correlate with symptoms relating to pneumonitis, which occurs faster than radiation-induced lung fibrosis. Radiation pulmonary fibrosis can occur 3 months to 1 year after radiation therapy. Treatments include exercise, medications used for patients with COPD, and oxygen.

7.1.7 Fistula formation

Radiation fistula formation between the trachea/bronchus and esophagus is a potential late-side effect of radiation therapy to the thorax. It is primarily due to injury of these hollow structures that is unable to be repaired by normal tissue repair mechanisms. It is a rare complication in the modern era of therapeutic radiation therapy. General time course for radiation-induced fistula formation is 6 months to 2 years after treatment. Main treatment option is surgical intervention and repair.

8.0 STUDY CALENDAR

	Pre-study	Pre-RT	RT	Follow-up (in time post- RT)									
				1 Day	1 Wk (+/- 7 days)	1 Mo (+/- 7 days)	3 Mo (+/- 2 wks)	6 Mo (+/- 2 wks)	9 Mo (+/- 2 wks)	12 Mo (+/- 2 wks)	15 Mo (+/- 2 wks)	18 Mo (+/- 2 wks)	21 Mo (+/- 2 wks)
SABR*			x										
Informed Consent	x												
Demographics	x												
Medical History	x												
Initial consultation	x												
Electrophysiology Confirmed Refractory VT	x												
Treatment Planning: CT and MRI		x											
Imaging: Cardiac MRI to Visualize Target		x											
Blood Samples		x		x	x	x	x			x			
Follow-up visit				x	X	x	x	x	x	x	x	x	x
QOL Questionnaire (SF-36)	x			x	x	x	x	x	x	x	x	x	x

*SABR: Stereotactic Ablative Radiotherapy

9.0 DATA REPORTING/REGULATORY CONSIDERATIONS

9.1 Monitoring Plan

Any potential adverse events will be discussed at the monthly internal study team meeting, led by the principal investigator.

9.2 Data Management

The principal investigator and research coordinator will be responsible for the database records of patient data. The data will be kept on the research coordinator's computer under password protection. A chart with all the relevant research patient information will be maintained for each patient by the research coordinator.

9.3 Confidentiality

Study data will be maintained in password protected computer files. Only research personnel will have access to this information. When possible, identifiers will be removed. Only research personnel and investigators will keep the study data along with identifiers together in the same database under password protection accessible.

10. STATISTICAL CONSIDERATIONS

10.1 Study Design and Objectives

This is a single arm, phase Ib/2a dose escalation study with an expansion cohort with the primary objectives of determining the maximal tolerated dose (MTD) for stereotactic ablative radiotherapy of targets in the cardiac myocardium and assessing the preliminary efficacy of the treatment for the control of ventricular arrhythmia. The secondary objectives are to determine the treatment impact on overall cardiac function (ejection fraction), on quality of life, on overall survival and to assess treatment-related toxicity by serum markers, imaging, and histology.

The dose escalation will be guided by Time-to-Event Continual Reassessment Method (TITE-CRM) [17] to ensure more patients will be spared dose limiting toxicities and more patients will be entered on the dose level that will be chosen as minimal dose of maximal effect. This design also allows for continual accrual of patients when delayed adverse events may be observed.

10.2 Sample Size and Power Considerations

10.2.1. Phase Ib dose-escalation portion:

A dose escalation design based on TITE-CRM will be used for this phase. A sample size of 22 patients will be used. We will investigate five different dose levels (15Gy x 1, 20Gy x 1, 25Gy x 1, 30Gy x 1, 35Gy x 1). The main advantage of TITE-CRM is that one can update the best guess regarding the optimal dose by using all the information accrued during the study. This method also incorporates the time to toxicity for each patient to avoid prolonged trial suspension while patients are being observed for late-onset toxicities.

We will start at a low initial dose 15Gy to ensure a maximum number of patients treated in a wide range of the dose-probability curve. We will only allow one-step escalation at a time and one patient at each step. Specifically, suppose that our targeted MTD of SABR is the dose level associated with a 20% probability of dose-limiting toxicity (DLT). Each of the five dose levels will

be assigned with prior guesses of DLT probabilities (0.02, 0.05, 0.10, 0.15 and 0.20, respectively) according to the investigator's experience and results from previous studies [13, 15, 16]. A one-parameter logistic model with fixed scale parameter equals to 3 will be chosen to fit the does-toxicity curve. The logarithm of the model parameter is assumed to follow a normal distribution with mean of 0 and standard deviation of 0.3. Starting with patient treated at the lowest dose (15Gy X 1), the posterior DLT probability of each dose level based on the logistic model will be re-estimated after each new patient inclusion. We will choose the dose level with the updated posterior success probability closest to our target DLT rate (20%) to administrate to the next patient. The process will continue until the exhaustion of the proposed sample size, and the dose with the posterior DLT probability closest to 20% will be selected as the MTD. Meanwhile, we will closely monitor adverse events and other safety endpoints.

Monte Carlo simulations were used to assess the operating characteristics of this design. 1000 trials were simulated using 3 different assumptions about the true probabilities of DLT at each dose: A) same as the prior probabilities; B) somewhat more toxic than the prior probabilities; C) more toxic than the prior probabilities with significant increase in toxicity between doses 30Gy and 35Gy. Among the operating characteristics considered in the sample size were the expected number of DLTs, the probability of selecting the correct dose (that associated with a 20% probability of DLT) as the target dose at the end of the trial, the time required to complete the trial, and the number of patients treated at or near the target dose. Sample sizes from 20 to 30 were evaluated, as were different rates of patient accrual. A sample size of 22 patients was determined to have acceptable probability of correctly selecting a dose with acceptable toxicity and enough patients treated about the target dose for characterization of the efficacy endpoints, while being feasible for completion within 25 months. The simulation results based on n=22 patients are shown in Table 1:

Table 1: Operative Characteristics of TITE-CRM Design

Dose-toxicity curve (logistic model): Pr(DLT at dose Xi)=exp[3+exp(beta)Xi]/[1+ exp[3+exp(beta)Xi], where beta~ Normal(0,0.3)					
	Scenario A				
proposed doses	15Gy	20Gy	25Gy	30Gy	35Gy
true probability of toxicity	0.02	0.05	0.1	0.15	0.2
prior probability (guess) of toxicity	0.02	0.05	0.1	0.15	0.2
probability of a dose being selected as the MTD	0.001	0.01	0.11	0.22	0.66
average number of patients treated at this dose level	1.0	1.6	3.3	4.3	11.8
average number of DLTs at this dose level	0.0	0.1	0.3	0.7	2.3
	Scenario B				
proposed doses	15Gy	20Gy	25Gy	30Gy	35Gy
true probability of toxicity	0.04	0.1	0.2	0.3	0.4

prior probability (guess) of toxicity	0.02	0.05	0.1	0.15	0.2
probability of a dose being selected as the MTD	0.01	0.18	0.45	0.26	0.10
average number of patients treated at this dose level	1.3	4.3	7.3	4.7	4.4
average number of DLTs at this dose level	0.1	0.4	1.5	1.4	1.7
	Scenario C				
proposed doses	15Gy	20Gy	25Gy	30Gy	35Gy
true probability of toxicity	0.08	0.2	0.35	0.5	0.7
prior probability (guess) of toxicity	0.02	0.05	0.1	0.15	0.2
probability of a dose being selected as the MTD	0.14	0.62	0.23	0.01	0.001
average number of patients treated at this dose level	3.5	9.6	6.0	1.9	1.1
average number of DLTs at this dose level	0.3	1.9	2.1	1.0	0.7

Note: The dose-toxicity curve is assumed to follow a logistic model as stated in the table. The true probabilities of DLT vary in three different scenarios, while the prior probabilities are the same. The target probability for DLT is 0.2. For each scenario, 1000 trials are simulated. In each trial, a total of 22 subjects are used. The trial starts at the lowest dose and only allows one dosage escalation at a time. The design assumes an accrual rate of one patient per month and a 3-month observed window for DLT. The study duration is estimated to be 25 months.

10.2.2. Phase IIa expansion portion:

The primary objective of the expansion phase is to assess the preliminary efficacy of the treatment by evaluating the ICD shock free survival rate at 6 months. Approximately 8 additional patients will be enrolled at the MTD. Based on the simulation results in Table 1, a total of 16-20 patients (8-12 patients in the dose escalation cohort and 8 in the expansion cohort) will be used to further assess toxicity, ICD shock free survival rate, overall survival, quality of life and overall cardiac function. Literature suggest 6-month ICD shock free survival rate is about 50%[6, 8, 9]. Assuming the proposed SABR treatment will yield 6-month ICD shock free survival rate of 80%, a sample size of 16 patients achieves 80% power to detect a 30% difference in 6-month ICD shock free survival, using a one-sided one-sample exact Binomial test, at a 0.10 significance level.

10.3 Planned Methods of Analysis

10.3.1 Analysis of Primary Endpoints

10.3.1.1 Analysis of Dose-Limiting Toxicities

The primary endpoint in Phase Ib portion is to either reach the MTD or a total dose of 35Gy. Toxicity will be graded using the NCI Common Toxicity Criteria for Adverse Events (CTCAE) v. 4.0. A dose-limiting toxicity (DLT) is any treatment-related grade 3, 4, or 5 toxicities in the following categories: gastrointestinal, cardiovascular, pulmonary, neurologic, or constitutional symptoms OR any other grade 4 or 5 toxicity attributed to the therapy. All reported DLTs will be

verified by the principal investigator, DSMB as independent review before final determination that a DLT has occurred. The study will close when either of the following events occurs: 1) the MTD is reached, or 2) the highest protocol dose level is treated and tolerated (a prescribed dose of 35Gy)

10.3.1.1 Analysis of Preliminary Efficacy

The primary endpoint in Phase IIa portion is ICD shock free survival rate at 6 months. For patients treated at MTD, we will calculate the ICD shock free rate and the corresponding 95% confidence interval.

10.3.2 Analysis of Secondary Endpoints

1) Incidence of salvage definitive anti-arrhythmia therapy (cardiac transplant) will be calculated and tabulated;

2) Incidence of return of ventricular tachycardia requiring defibrillation, intravenous drug therapy or readmission to hospital will be calculated and tabulated;

3) Incidence of ICD shocks in the periods of 3,6 and 12 months pre and post the SABR procedure will be calculated and tabulated;

4) Incidence of decline of LV ejection fraction by more than 5% on two consecutive echocardiograms will be calculated and tabulated;

5) Incidence of persistent increase in baseline supplemental oxygen requirement by 1L for a duration of >3 months will be calculated and tabulated;

6) Incidence of Use of steroids for radiotherapy related indications

7) Overall survival will be estimated by Kaplan-Meier method. Summaries of the number and percentage of patients who have died, are still in survival follow-up, are lost to follow-up and have withdrawn consent will be provided along with median overall survival.

8) The score of quality of life questionnaire will be summarized at each time point and comparison of pre- and post-treatment scores will be carried out by non-parametric Wilcoxon sign-rank test.

10.3.3 Safety Analysis

Overall exposure to study agent, the numbers of patients completing the study, and the dose intensity will be summarized using descriptive statistics. Serum markers, imaging, and histology will be assessed throughout the study period for toxicity. AEs and SAEs will be reported using a CTCAE v4.0 terminology and severity.

10.4 Interim Analysis

Interim reports will be prepared every six months until the results of the study are published. In general, the interim reports will contain information about patient accrual rate with projected completion dates, status of QA review and compliance rate of treatment per protocol, and the frequencies and severity of toxicity.

11. References

1. Zheng, Z.J., et al., *Sudden cardiac death in the United States, 1989 to 1998.* Circulation, 2001. **104**(18): p. 2158-63.
2. Chugh, S.S., et al., *Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community.* J Am Coll Cardiol, 2004. **44**(6): p. 1268-75.
3. Yung, D., et al., *Survival after implantable cardioverter-defibrillator implantation in the elderly.* Circulation, 2013. **127**(24): p. 2383-92.
4. Bayes de Luna, A., P. Coumel, and J.F. Leclercq, *Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases.* Am Heart J, 1989. **117**(1): p. 151-9.
5. *Strategies to improve cardiac arrest survival : a time to act*. 2015, Washington, DC: National Academies Press. pages cm.
6. Stevenson, W.G., et al., *Irrigated radiofrequency catheter ablation guided by electroanatomic mapping for recurrent ventricular tachycardia after myocardial infarction: the multicenter thermocool ventricular tachycardia ablation trial.* Circulation, 2008. **118**(25): p. 2773-82.
7. Tanner, H., et al., *Catheter ablation of recurrent scar-related ventricular tachycardia using electroanatomical mapping and irrigated ablation technology: results of the prospective multicenter Euro-VT-study.* J Cardiovasc Electrophysiol, 2010. **21**(1): p. 47-53.
8. Ajijola, O.A., et al., *Bilateral cardiac sympathetic denervation for the management of electrical storm.* J Am Coll Cardiol, 2012. **59**(1): p. 91-2.
9. Ajijola, O.A., et al., *Bilateral cardiac sympathetic denervation: why, who and when?* Expert Rev Cardiovasc Ther, 2012. **10**(8): p. 947-9.
10. Sharma, A., et al., *Noninvasive stereotactic radiosurgery (CyberHeart) for creation of ablation lesions in the atrium.* Heart Rhythm, 2010. **7**(6): p. 802-10.
11. Sullivan, R.M. and A. Mazur, *Stereotactic robotic radiosurgery (CyberHeart): a cyber revolution in cardiac ablation?* Heart Rhythm, 2010. **7**(6): p. 811-2.
12. Blanck, O., et al., *Dose-escalation study for cardiac radiosurgery in a porcine model.* Int J Radiat Oncol Biol Phys, 2014. **89**(3): p. 590-8.
13. Videtic, G.M., et al., *30 Gy or 34 Gy? Comparing 2 single-fraction SBRT dose schedules for stage I medically inoperable non-small cell lung cancer.* Int J Radiat Oncol Biol Phys, 2014. **90**(1): p. 203-8.
14. Evans, J.D., et al., *Cardiac (1)(8)F-fluorodeoxyglucose uptake on positron emission tomography after thoracic stereotactic body radiation therapy.* Radiother Oncol, 2013. **109**(1): p. 82-8.
15. Cvek, J., Neuwirth, R., Knybel, L., Molenda, L., Otahal, B., Pindor, J., Murarova, M., Kodaj, M., Fiala, M., Branny, M., Feltl, D., *Cardiac Radiosurgery for Malignant Ventricular Tachycardia.* Cureus, 2014. **6**(7).
16. Loo, B.W., Jr., et al., *Stereotactic ablative radiotherapy for the treatment of refractory cardiac ventricular arrhythmia.* Circ Arrhythm Electrophysiol, 2015. **8**(3): p. 748-50.
17. Cheung, Y.K. and R. Chappell, *Sequential designs for phase I clinical trials with late-onset toxicities.* Biometrics, 2000. **56**(4): p. 1177-82.