MC1723 / 17-008401

Characterizing Chemo-Radiotherapy Treatment-Related Cardiac Changes

NCT04183218

Document Date: 02/12/2024

Mayo Clinic: Department of Radiation Oncology

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Study Principal Investigator: [redacted]

Study Co-investigators: [redacted]

Imaging Co-investigators: [redacted]

Biomarkers Co-investigator: [redacted]

Co-Investigators: [redacted]

Statistician: [redacted]

√Study contributor(s) not responsible for patient care

Document History

Version 1	October 18, 2018
Version 2	February 18, 2019
Version 3	August 2, 2019
Version 4	August 27, 2019
Version 5	April 7, 2020
Version 6	July 8, 2021
Version 7	April 18, 2022
Version 8	February 12, 2024

Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, protocol document, consent form, regulatory issues, forms completion and submission, adverse events, forms completion and submission	[redacted]

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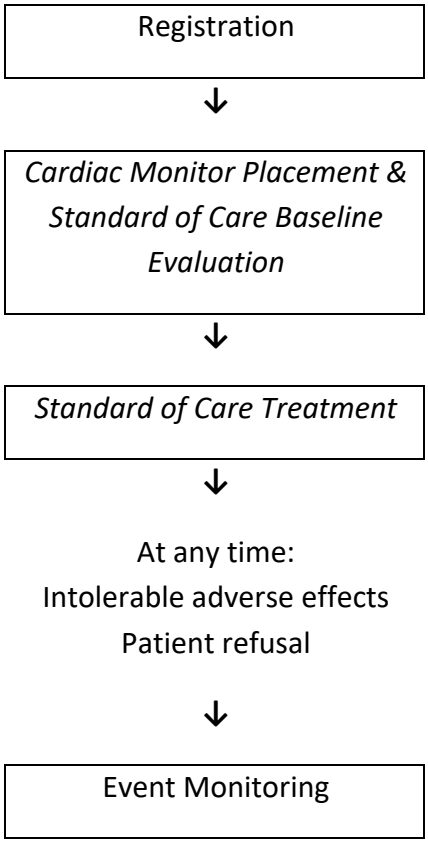
Study Schema



List of Abbreviations

AE	Adverse Event/Adverse Experience
ARDS	Acute Respiratory Distress Syndrome
AV	Atrioventricular
CAD	Coronary Artery Disease
CFR	Code of Federal Regulations
CRF	Case Report Form
CRT	Chemoradiotherapy
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
Fx	Fractions
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
LRC	Local Regional Control
ICM	Insertable Cardiac Monitoring
IMRT	Intensity-Modulated Radiotherapy
IRB	Institutional Review Board
IV	Intravenous
MRI	Magnetic Resonance Imaging
OS	Overall Survival
PBS	Pencil Beam Scanning
pCR	Pathologic Complete Response
PFS	Progression Free Survival
PHI	Protected Health Information
PI	Principal Investigator
PRO	Patient Reported Outcomes
QOL	Quality of Life
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event/Serious Adverse Experience
SBRT	Stereotactic Body Radiation Therapy
SOC	Standard of Care
SCD	Sudden Cardiac Death
SOP	Standard Operating Procedure

1.0 Background

1.1 Condition to be studied

We plan to characterize cardiotoxicity after radiotherapy (RT) for lung and esophageal cancer.

1.2 Therapy

Therapy will be standard of care (SOC) at the discretion of the treating physician.

1.3 Study Rationale

Combined radiation and chemotherapy is an integral part of the treatment of thoracic malignancies. However, for cancers in close proximity to the heart, excess radiation to cardiac tissue may be unavoidable in order to achieve the desired dose to the cancer. Irradiated cardiac tissue may develop permanent damage, decreasing the overall benefit of chemoradiation (CRT). For example, Radiation Therapy Oncology Group (RTOG) 0617 (Bradley Lancet Oncol 2015) showed a decreased median survival for higher compared to lower radiation doses in the treatment of non-small cell lung cancer with CRT. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Meta-Analysis (EBCTCG Lancet 2014) showed a relative decrease in overall survival of 23% for breast cancer patients with negative axillary dissection that received post-mastectomy RT. However, in the same study, an 11% relative benefit was seen for lymph node positive patients treated with RT. The practice changing Cross Trial (van Hagen N Engl J Med 2012) showed a large survival benefit despite employing lower RT dose than previous trials. The large survival benefit from CRT seen for esophageal cancer patients in this trial could have been related to lower cardiac radiation exposure.

To develop heart-saving treatment strategies, it is imperative to improve our understanding of early cardiac damage and its association with fatal events occurring within the first year after treatment. Unfortunately, this is currently an unmet need, as we poorly understand early cardiac damage due to CRT, especially for lung and esophageal cancer. This area of study is significant since treatment-related mortality decreases the substantial survival benefit that treatment otherwise confers to patients with various cancers. More importantly, the pathophysiologic mechanism of these potential fatal cardiac events is unknown. A recent study of early lung cancer patients treated with SBRT indicated that RT dose to the superior vena cava and left atrium show the greatest association with survival (Stam ESTRO Abstract 2016), suggesting cardiac conduction disorder as the etiology of treatment-related mortality. Furthermore, a pooled analysis of dose-escalation trials in locally advanced lung cancer showed about 10% symptomatic arrhythmia at 2 years (Wang J Clin Oncol 2017), and high-dose cardiac

radiation has been shown to ablate ventricular tachycardia (Cuculich N Engl J Med 2017). Given this growing body of evidence, SCD due to cardiac conduction disorders could account for the unexplained increased mortality on the high-dose RT arm of RTOG 0617. Unfortunately, cardiac conduction disorders are often transient and asymptomatic. For example, up to 90% of atrial fibrillation can be asymptomatic (Verma JAMA Intern Med 2013, Strickberger Heart Rhythm 2005, Orlov Pacing Clin Electrophysiol 2007). This makes identifying cardiac conduction disorder as a cause of SCD exceedingly difficult. As reviewed in section 1.3, ICM allows for continuous highly sensitive cardiac rhythm monitoring and the unique opportunity to record cardiac conduction leading up to and including the time of death after RT.

Timeline of Events

The currently established paradigm for cardiotoxicity after radiotherapy involves long-term vascular changes that increase the risk of coronary artery disease (CAD). However, extensively evaluated cohorts of patients have demonstrated only minimal increase in cardiac death associated with radiation induced CAD (van den Bogaard J Clin Oncol 2017). In this recent study, only 30 out of 910 patients (3.3%) developed adverse coronary event during 9-year follow-up, 10 of whom died of ischemic heart disease. Their model estimated only 1.13% excess cumulative risk of adverse coronary event related to RT, indicating that 10 of the aforementioned 30 adverse coronary events could be attributed to RT. This translates to about 3 deaths in 910 patients (0.3%) due to RT-related CAD. Unfortunately, RTOG 0617 demonstrated over 10% absolute decrease in overall survival by 12 months for lung cancer patients receiving a modest 14 Gy increase in RT dose (Bradley Lancet Oncol 2015). The EBCTCG meta-analysis showed a relative decrease of 23% for node-negative breast cancer patients receiving post-mastectomy RT (EBCTCG Lancet 2014). The Cross Trial doubled the median overall survival with the use of smaller RT fields and a 10 Gy reduction in RT dose (van Hagen N Engl J Med 2012). Clearly, survival differences of these magnitudes cannot be accounted for by RT-related CAD.

Interestingly, in RTOG 0617, the separation between the survival curves for the high and low-dose arms began to accelerate at about 6 months and stabilized at about 12 months, with approximately 10% absolute difference in overall survival. This difference remained relatively constant for the remainder of the follow-up period. Thus, the excess death on the high-dose arm of RTOG 0617 occurred within 12 months. The definitive cause of these deaths was not detected or explained by the patients' medical records or follow-up monitoring with the trial. However, secondary analysis of RTOG 0617 revealed strong association between overall survival and the volume of heart receiving 40 Gy (V40) (Chun J Clin Oncol 2017). Therefore, the excess mortality associated with thoracic RT is likely cardiac in nature.

Sudden cardiac death without any other signs or symptoms is usually related to electrophysiological changes in the heart. To ensure that we capture these events, we plan for continuous monitoring of cardiac conduction using implanted cardiac monitors. Information can be uploaded daily and events appropriately managed per standard of care.

Summary

Large observational studies provide further information regarding the effectiveness and safety of thoracic RT in a more generalized population of patients.

To address the specific objectives of this study, a longitudinal observational approach will allow comprehensive characterization of the electrophysiological cardiac changes in non-metastatic, non-recurrent lung and esophageal cancer patients who are receiving thoracic radiotherapy.

We propose an innovative and exploratory study on early cardiac toxicity and permanent cardiac damage after CRT for esophageal and lung cancer by using continuous ambulatory cardiac monitoring with an implanted cardiac device. Standard of care cardiac monitoring would be done by our cardiology group including echocardiography and MRI, and other necessary medical procedures as seen clinically necessary. Bio-banking of whole blood samples for future correlative biomarker studies would be done. Dried blood spots for RNA analysis would provide additional correlative data. We have formed a multidisciplinary team with radiation oncologists, radiologists, cardiologists, a cancer geneticist, and imaging scientists to evaluate this important question.

Although this is an observational study, findings seen with the implanted cardiac monitor can be addressed as part of the routine medical care of these patients, addressing cardiac conduction changes that otherwise may have been fatal.

Our hope is that we can identify potentially fatal radiation induced cardiac changes that otherwise would remain unnoticed, facilitate the treatment of these early cardiac changes as part of the standard of care, and therefore prevent RT-related cardiac death.

1.4 Rationale on any research related tests being done

Insertable Cardiac Monitoring: In a recent multi-national, multi-institutional study, RT dose to the superior vena cava and left atrium was significantly associated with survival after lung stereotactic body RT (Stam ESTRO Abstract 2016). Sudden cardiac death (SCD), particularly as caused by cardiac conduction disorders, is a potential culprit when considering the fatal events that may originate in the superior vena cava or atria and may account for the otherwise unexplained mortality associated with cardiac dose in recent clinical trials of thoracic RT. To identify potential SCD after thoracic RT that has

thus far been unappreciated, we need a more sensitive test. Insertable cardiac monitors (ICM) are small wireless cardiac devices placed under the skin in the chest area by a minimally invasive technique. ICM are used for long-term heart rhythm monitoring of patients with suspicion of rare or infrequent rhythm abnormalities that are unlikely to be diagnosed with short-term monitoring. These devices have been studied in the investigation of atrial fibrillation, cryptogenic stroke, syncope, and post-myocardial infarction SCD. The Medtronic Reveal LINQ™ ICM has 99.4% accuracy for atrial fibrillation detection (Sanders Heart Rhythm 2016). In the year after cryptogenic stroke, ICM finds 7.3x more atrial fibrillation than conventional follow-up (Sanna N Engl J Med 2014). After ablation of atrial fibrillation, ICM detects more recurrent arrhythmia than conventional monitoring, which would miss at least 61% of recurrent arrhythmia (Kapa J Cardiovasc Electrophysiol 2013). In unexplained recurrent syncope or pre-syncope, ICM helped establish cardiac etiology in 75% of patients (Edvardsson Europace 2011). Furthermore, ICM is significantly cheaper per patient and per diagnosis for unexplained syncope than conventional testing with external loop recorder, tilt testing, and electrophysiologic testing (Krahn J Am Coll Cardiol 2003). The expanded role of ICM as "biological monitors" helping to understand mechanisms of SCD in special populations has also been established (Gang Europace 2010, Bloch Thomsen Circulation 2010). In patients after acute myocardial infarction with ejection fraction ≤ 40%, ICM demonstrated a high incidence of brady and tachyarrhythmia and an association of high degree atrioventricular (AV) block with SCD. Post-mortem interrogation of ICM showed ventricular tachycardia/fibrillation (VT/VF) and bradyarrhythmia each accounting for half of the events at the time of death. ICMs can remain in place for the duration of the study.

Whole Blood Biobanking: Whole blood samples will be obtained via peripheral blood draw at time-points corresponding to SOC clinic appointments: prior to RT initiation, 4 weeks after RT completion, 3 months after RT completion, 9 months after RT completion, and 12 months after RT completion. The samples will be stored for future biomarker studies to be correlated with cardiac conduction and imaging findings.

Dried Blood Spot Biomarker Analysis: In conjunction with the above-mentioned whole blood biobanking and biomarker studies, we plan to obtain a dried blood spot on filter paper at time-points corresponding to SOC clinic appointments: prior to RT initiation, 4 weeks after RT completion, 3 months after RT completion, 9 months after RT completion, and 12 months after RT completion. We have developed RNA sequencing approaches using nucleic acid isolated from single drops of dried blood. The collection of dried blood spot can be done at home by the patient using an approach analogous to finger prick blood glucose checks used by millions of patients with diabetes. This novel approach to RNA biomarker profiling may identify novel nucleic acid signatures associated with cancer treatment induced cardiac toxicity and provides a

potentially powerful correlate to standard whole blood biobanking and biomarker studies.

1.5 Description of the Study

This is an observational study designed to follow non-metastatic, non-recurrent lung and esophageal cancer patients who are receiving thoracic radiotherapy.

Patients will be followed prospectively in the PCG-registry, through a separate consent. The only testing (beyond standard of care evaluation) for the current study would include ambulatory arrhythmia monitoring with ICM, whole blood samples to be biobanked for future biomarker studies, and dried blood spot collection for RNA analysis..

Approximately 24 patients total will be enrolled.

Please refer to the UCM Procedural/Treatment Guidelines for (Disease)/ AZ treatment guidelines. No study-specific visits or evaluations will be required. Patients will be evaluated according to the physician's standard practice and discretion. Patient data will be drawn from the patients' medical records. Patients will be considered "on study" until one year after completion of RT, withdrawal of consent, lost to follow-up, or study closure, or death

1.6 Rationale for Study Design

Large observational studies provide further information regarding the effectiveness and safety of thoracic RT in a more generalized population of patients.

To address the specific objectives of this study, a longitudinal observational approach will allow comprehensive characterization of the electrophysiological cardiac changes following thoracic RT.

Patients' cardiac conduction will be monitored constantly by the electrophysiology lab as part of the standard of care.

2.0 Goals

This is an observational study designed to follow non-metastatic, non-recurrent lung and esophageal cancer patients who are receiving thoracic radiotherapy. However, even with the relatively small sample size, we can assess the value and utility of continuous ambulatory arrhythmia monitoring with an implanted cardiac device and correlate findings with SOC cardiac follow-up, imaging, and biomarker analysis on biobanked whole blood samples. Our findings can help achieve the following objectives:

2.1 Primary Goal

2.11 To determine the 12-month cardiac event rate as defined in section 11.1 after radiation or chemo-radiation for the treatment of lung or esophageal cancer.

2.2 Exploratory Goals

2.21 Define the spectrum of cardiac toxicity among CRT patients at highest risk of cardiac toxicity.

2.22 Establish the timeline of cardiac toxicity development and identify early predictive findings of permanent damage.

2.23 Characterize the areas of the heart at highest risk for persistent cardiac damage.

2.24 Identify a dose response threshold for RT damage in different areas of the heart.

2.25 Improve survival by alerting the cardiology team of the need for life-saving standard of care interventions. If we can show that excess RT-related deaths are related to electrophysiological changes, life-saving strategies may be possible.

2.26 Describe medical interventions employed for the cardiac events identified in the study.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 Planned standard of care curative thoracic RT or CRT with anticipated heart V40 > 20cc (At least 20cc of the heart should receive a dose of 40Gy or higher)

3.13 Able to follow-up at all specified standard of care time-points.

3.14 Patients can receive treatment as part of the standard of care or in a different study.

3.15 Receiving radiation treatment to an area close to the heart, for example gastroesophageal junction cancer, hilar lung cancer, or mainstem bronchus lung cancer.

3.16 Any type of systemic therapy or surgery before during or after radiation is acceptable

3.17 Prior Radiation to other areas is acceptable.

3.18 Planned radiation doses equal or higher than 40Gy

3.2 Exclusion Criteria

3.21 Metastatic disease.

3.22 Recurrent disease.

3.23 Patient receiving radiation prescription doses lower than 40 Gy.

3.24 No prior radiation that included any part of the heart is acceptable

3.25 No thoracic re-irradiation

4.0 Test Schedule

- Implanted cardiac monitors would be placed prior to starting radiation treatments and monitored for 12 months after treatment (for a total of 14 months). Baseline recordings of the cardiac rhythm would be done prior to RT, 4 weeks post-RT, 3 months post-RT, 9 months post-RT, and 12 months post-RT.
- Blood bio-banking would be done as seen in Appendix 1: prior to RT, 4 weeks post-RT, 3 months post-RT, 9 months post-RT, and 12 months post-RT.
- Dried blood spot would be collected at home by the patient prior to RT, 4 weeks post-RT, 3 months post-RT, 9 months post-RT, and 12 months post-RT.
- All patients will complete SOC treatment as defined by his treating oncologists including evaluation by cardiology and cardiac MRI evaluations.
  SOC procedures are highlighted in blue—they are considered standard for the care for this patient population and currently done in the Cardio-Oncology Clinic at Mayo Clinic in Arizona. All SOC procedures are recommended, but may be omitted at the discretion of the physician or patient.
- Cardiac MRI information may be shared with ASU for additional MRI post processing. De-identified images or raw MRI data will be used.

Table 5.0			Post-Tx[5]				
	PRE-TX (-120 to 0 days prior to Tx)	TX	4 weeks (+/- 2 WEEKS)	3 months (+/- 6 WEEKS)	9 months(+/- 6 WEEKS)	12 months (+/- 6 WEEKS)	Unscheduled
Procedures							
Informed Consent	X						
Cardiology evaluation	X						X[1]
Cardiac history	X						
12-lead ECG	X			X			X
Holter monitor, if clinically indicated	X						X
2 D transthoracic ECHO	X[7]			X			X

Cardiac Labs (troponin, CK, CKMB, pro-BNP,BMP, CBC)	X		X	X	X	X	X
Implanted cardiac monitor[r6]	X[7]						
Explant cardiac monitor[r6]							X
Cardiac recordings via implanted cardiac monitor[r6]	X[7]		X	X	X	X	X
SOC RT Treatment [2]		X					
ECOG	X						X
AE	X	X	X	X	X	X	X
Bio-banking(blood)[r]	X		X	X	X	X	
Dried blood spots (TGEN)[r]	X		X	X	X	X	
Cardiac MRI[r]	X[3, 7]			X[3]		X[3]	
Pulmonary Function Test	X[4]					X	

[1] Additional cardiac follow-up visits as clinically indicated per standard of care treatment.

[2]Additional radiation oncology follow-up visits; scheduled per standard of care treatment.

[3]Cardiac MRI as clinically indicated as per SOC cardiology evaluation; however study will pay for all patients as a research cost.

[4]Pulmonary function tests obtained pre-treatment (within 6 months of the start of treatment)

[5]Time is measured from the date radiation therapy is completed.

[6]Patient care costs covered by Mayo Clinic Cardiology

[7]Highly recommended before the start of RT. If this is not clinically possible due to scheduling, conduct as soon as possible after the start of RT

[r]Indicates paid by research

After enrollment and prior to initiation of RT or CRT, cardiac testing will be per SOC at our Cardio-Oncology Clinic (e.g. ECG, strain echocardiography, cardiac MRI). Pulmonary function tests would also be obtained per SOC. ICM will be inserted subcutaneously by a cardiologist in the left para-sternal area, using standard sterile technique with local anesthesia. Risks of this insertion are truly minimal but may include bleeding or infection. For reference, this in-office minimally invasive procedure is analogous to the upper arm Implanon/Nexplanon® birth control implant. Whole blood samples will be drawn via peripheral blood draw and biobanked. Dried blood spots will be collected at home by patients and returned for analysis. For reference, the approach for dried blood spot collection is analogous to a finger prick blood glucose check. Dried blood spot collection would only require a single finger prick at each time point and would be truly minimal risk but may carry very low risk of infection. STANDARD OF CARE cardiac testing, STANDARD OF CARE pulmonary function tests, and peripheral blood draw for whole blood biobanking will be performed at STANDARD OF CARE follow-up appointments after RT, including 4 weeks after RT, 3 months after RT, 9 months after RT, and 12 months after RT. Data from the ICM will be collected via wireless data transfer. Data will be transferred on scheduled monthly remote follow-ups or unscheduled in case there is a rhythm alert notification automatically sent (when the arrhythmia event meets pre-determined criteria). The follow-up data will be monitored by the Mayo Clinic Cardiac Implantable Electronic Devices Remote Follow-up Clinic. Alerts from any devices are monitored within 24 hours, 365 days per year uninterrupted. All abnormal cardiac rhythm strips are initially adjudicated by a Certified Cardiac Device Specialist Registered Nurse and confirmed by a cardiac electrophysiologist. The programmed criteria for automatic arrhythmia storage is: sinus bradycardia ≤ 30 bpm for ≥ 8 seconds, sinus arrest with pauses ≥ 4.5 seconds, and 2nd or 3rd degree degree AV block ≤ 30 bpm lasting ≥ 8 seconds. Tachycardia is defined as a heart rate ≥ 150 bpm for ≥ 16 beats. Sustained VT is defined as lasting ≥ 30 seconds. Post-mortem device interrogation will be performed in cases of patient death. Patients will undergo limited chest autopsy, if they agree and consent.

4.1 Event Monitoring/Survival Follow-up

Patients will be “on study” until one year after completion of RT, withdrawal of consent, lost to follow-up, study closure, or death.

5.0 Stratification Factors OR Grouping Factor: None

6.0 Registration/Randomization Procedures

6.1 Registration

Patient will be registered to the study when they have consented, met eligibility criteria and have been logged into the Research Participant Tracking System (Ptrax).

6.11 Verify the following procedures are completed prior to Registration to the study.

6.12 IRB approval at the registering institution

6.13 Existence of a signed informed consent

6.14 Patient eligibility complete

Note: Radiation Therapy on this protocol must be performed at Mayo Clinic Arizona under the supervision of a radiation oncologist.

7.0 Protocol Treatment

7.1 Standard Treatment (Per UCM Procedural/ Treatment Guidelines for lung and esophageal cancer/Mayo Clinic treatment guidelines).

Esophageal

[redacted]

Lung

[redacted]

8.0 Dosage Modification Based on Adverse Events

8.1 Treatment delivered as per SOC. No changes to the SOC will be done during this study (Per UCM Procedural/ Treatment Guidelines for lung and esophageal cancer/Mayo Clinic treatment guidelines; see section 7.1).

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) current version 5.0* unless otherwise specified*** ← ←

9.0 Ancillary Treatment/Supportive Care: None, except as indicated per SOC.

10.0 Adverse Event (AE) Monitoring and Reporting

10 .1 Definitions

10. 11 Adverse Event: Any untoward medical occurrence associated with standard of care treatment involved in this study.

10.12 Serious Adverse Event: Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- Death
- Life threatening adverse experience
- Hospitalization
- Inpatient, new, or prolonged; disability/incapacity
- Persistent or significant birth defect/anomaly

or problems/events that in the opinion of the sponsor investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially comprised the research data. All adverse events that do not meet any of the criteria for serious, should be regarded as non-serious adverse events.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)- Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data,

  AND

- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent

document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND

- Related: A problem or event is "related" if it is possibly related to the research procedures.
- Preexisting Condition- A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period. At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

10.12 Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

10.2 Recording Adverse Events/ Treatment being studied

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:

[redacted]

10.21 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 5.0. Next, determine whether the event is expected or unexpected and if the adverse event is related to the study procedure. With this information, determine whether the event must be reported as an expedited report (see Section 10.25).

Expedited and routine reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4 and 10.6. All expected AE reports must also be sent to the local Institutional Review Board (IRB) according to local IRB's policies and procedures.

10.211 When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

Definite - The AE *is clearly related* to the agent(s)/procedure.

Probable - The AE *is likely related* to the agent(s)/procedure.

Possible - The AE *may be related* to the agent(s)/procedure.

Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.

Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

10.22 Exceptions to Expedited Reporting

An expedited report may not be required for specific Grade 1, 2 and 3 serious Adverse Events. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will supersede the standard Expedited Adverse Event Reporting Requirements**: Hospitalizations for reasons deemed to be disease or SOC related will not be reported.**

10.23 Solicited Adverse Events Grade 2 or higher:

Dyspnea
Conduction disorders
Chest pain/cardiac pain
Congestive Heart Failure
Myocardial infarction
Myocarditis
Pericardial effusion
Pericarditis
Lung Adverse Events
Gastrointestinal Adverse Events

10.3 Other Required Reporting

10.31 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related

documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

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

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note 1: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within.

Note 2: research procedures include: cardiac monitoring device placement and extraction, cardiac monitoring employing the cardiac monitoring device, cardiac MRI, dried blood collection, and blood biobanking. Cancer treatment is per SOC and at the discretion of the treating physicians and not part of the research procedures. Expected toxicities as part of the SOC cancer treatment will not be considered for IRB reporting.

10.32 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.5 Monitoring and Auditing

The investigator will permit study-related monitoring, audits, and inspections by the IRB, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices

10.51 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10.7 "Monitoring and Auditing"). Medical monitoring will include a regular assessment of the number and type of

serious adverse events. “Any serious adverse events will be followed up by the sentinel event reporting procedure”

10.52 Internal Data and Safety Monitoring Board

The trial will be reviewed by the Cancer Center Auditing area on a bi-annual or yearly basis dependent on random study selection to assess accrual, adverse events, and any endpoint problems. Any safety issues requiring protocol changes will be communicated through protocol amendments.

11.0 Treatment Evaluation/Measurement of Effect

This will be measured based on retrospective clinical outcomes.

11.1 Effectiveness Outcome Measures

Cardiac Events:

Any cardiac event after registration including electrophysiological changes as defined by the continuous insertable cardiac monitor (ICM); CHF; Miocardial infarction; pericarditis or myocarditis; cardiac ablation or cardiac pacemaker; cardiac stent placement or any coronary procedure for coronary damage; or any cardiac event as defined by the patients’ medical records or autopsy if done.

Cardiac event determined by the ICM would include: Bradycardia: asystole > 3 seconds, bradycardia HR < 40 bp; Tachy: HR > 150 bpm for any number of beats; Atrial Fibrillation lasting ≥ 8 seconds. Post-mortem device interrogation will be performed when possible in cases of patient death and included as per ICM criteria. Patients will undergo limited chest autopsy, if they agree and consent.

11.2 Safety Outcome Measures

In-office placement of the device with local anesthetic is very safe. Likewise, the device itself is very safe. Risks of this insertion are truly minimal but may include

bleeding or infection. We will monitor any adverse events related to the placement of the device.

11.3 This is an observational study designed to follow cardiac changes in patients with esophageal or lung cancer who receive curative SOC thoracic RT or CRT. Data regarding the adverse events per SOC, surgery, RT, chemotherapy, and regular standard of care follow-up will be observed and collected as part of the SOC.

11.4 A patient is deemed ineligible if he/she is removed from the study for any reason before any study data is obtained. On-study material and Cancel Notification/Termination Form must be completed in CRF. No further data submission is necessary. Subject will be replaced in accrual number.

11.5 If the subject participated in study, all data up until the point of confirmation of ineligibility must be submitted.

12.0 Descriptive Factors

3D radiation, IMRT, vs Proton therapy

Esophageal cancer, lung cancer, other thoracic malignancy

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient will go off study and continue in the monitoring phase.

- If the patient received MR and PET for radiotherapy planning, all data up until the point of confirmation of ineligibility must be submitted.

13.2 Those patients who will not receive any radiation treatment or who will receive radiation treatment elsewhere will go off study.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be Collected for this Protocol

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Before treatment, 4 weeks, 3 months, 9 months, and 12 months post treatment	Process at site?
Biobanking	*Mandatory*	*Whole blood*	*EDTA Tubes*	*10mL (1) in 1 mL aliquots*	*X*	*Yes - frozen*
Biobanking	*Mandatory*	*Blood; serum only*	*2 No additive tubes (for serum)*	*10mL (1) in 1 mL aliquots*	*X*	*Yes - frozen*
Biobanking	*Mandatory*	*Blood; plasma only*	*2 EDTA Tubes*	*6 mL in 1 mL aliquots*	*X*	*Yes - frozen*
RNA Analysis	*Mandatory*	*Dried Blood*	*Dried blood kit*	*5 – 10 drops*	*X*	*N/A*

14.2 Collection and Processing

Collected biobank samples will be drawn according to the test schedule and summary in Table 5.0. Collect and process pre-treatment, 4 weeks post-RT, 3 months post-RT, 9 months post-RT, and 12 months post-RT, blood/blood products according to the above table. Label specimen tube(s) with protocol number, study patient ID number, and time and date blood is drawn.

14.3 Shipping and Handling

14.31 Specimen Storage

BAP will process and store biobank specimens per standard operating procedures. Blood samples will be collected prospectively and stored until funding sources have been identified for molecular studies.

14.32 Shipping Specimens

No shipping for the collected biobank samples.

A dried blood kit provided by TGEN will be collected at Mayo Clinic Arizona during the pre-treatment visit. The study coordinator will assist the patient with instructions on how to take the sample and ship it to TGEN. The remaining collection time points (4 weeks, 3 months, 9 months, and 12 months post-treatment) will be collected by the participant at home and shipped to TGEN for analysis using a pre-paid shipping label included in the kit.

[redacted]

15.0 Drug Information

Not applicable

16.0 Statistical Considerations and Methodology

16.1 Study Design

This is a single-arm, observational study designed to determine the 12-month cardiac event rate after radiation or chemo-radiation for thoracic malignancies meeting the eligibility criteria.

16.11 Primary Endpoint:

A cardiac event will be defined according to section 11.1 and occurring during the first 12 months after radiation or chemo-radiation. An evaluable patient will be classified as a failure (cardiac event) for the primary endpoint if the patient had any of the events listed in section 11.1 during the time period. All patients meeting the eligibility criteria who have signed a consent form, have begun RT, and have not experienced a major treatment violation within the first month of treatment will be evaluable for response.

16.2 Statistical Design:

This is an observational study intended to provide preliminary estimates of cardiac event rate in patients receiving radiation or chemo-radiation. Safety of the implanted cardiac monitoring device will be described. Point estimates and two-sided 95% confidence intervals will be computed. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be included in the descriptive estimates.

16.22 Sample Size

The largest clinical benefit (detection of cardiac event) where the proposed cardiac monitoring device would be considered ineffective in this population is 1%, and the smallest clinical benefit rate that would warrant subsequent studies is 10%. With 18 patients, this study has 80%

power with a 1-sided alpha of 0.1 to test the null hypothesis that the event rate in the given population is at most 1%.

Assuming that about 10% of patients would be lost to follow-up or found ineligible and accounting for the approximately 20% death rate at 12 months in the standard arm of RTOG 0617, we would require a total sample size of 24 patients to fulfill those of the 6 necessary 18 possibly missing at 12 months.

16.23 Accrual Time and Study Duration

The anticipated accrual rate is approximately 2 patients per month. Therefore, the accrual period for this study is expected to be 12 months. Analysis can begin approximately 24 months after the trial begins, i.e., as soon as the last patient has been followed for up to 12 months.

16.24 Other Considerations

Adverse events, observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.3 Analysis Plan

The analysis for this trial will commence at the time the patients have become evaluable for the primary endpoint. Such a decision will be made by the Statistician and Study Chair, availability of data for secondary endpoints and the level of data maturity. Summary statistics will be presented for demographic and baseline clinical characteristic variables for all subjects. All continuous parameters will be summarized using standard summary statistics as appropriate (n, mean, standard deviation, median, minimum, maximum, 25th percentile, and 75th percentile). Summary statistics for categorical variables will include frequency counts and percentages. Summaries will be presented for all patients.

16.31 Primary Endpoint

Definition: The primary endpoint of this trial is cardiac event rate at 12 months as defined in Section 11.

16.312 Estimation: The proportion of failures (cardiac event) will be estimated by

the number of cardiac events divided by the total number of evaluable patients. Confidence intervals for the true success proportion will be calculated according to the exact Clopper – Pearson..

16.313 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals as though they were accrued in the final stage.

16.32 Definitions and Analyses of Secondary Endpoints

16.321 Analysis Plan
The analysis for this trial will commence when 24 patients have either died or reached the 12 month data point. Cardiac event as recorded in section 11.1 would be used for our analysis. We expect to see 3 or more cardiac events grade 3 or higher based on the CTC AE V5.0.

16.322 The following definitions are used for the secondary endpoints of interest:

All end points would be measured studied from the date of patient registration

- Acute adverse events: all AEs occurring within the first 6 months from the date of enrollment.
- Late adverse events: all AEs occurring after the first 6 months from the date of enrollment.
- Loco-regional recurrence: local recurrences of the cancer in the same location where the disease was found on any diagnostic or staging study.
- Distant recurrence: metastatic cancer that has either been biopsy confirmed or clinically diagnosed as recurrent.
- Disease- free survival: the time from study registration any local, regional, distant failure, or death.
- Cause specific survival: the time from registration to death due to cancer. If the cause of death is unknown or difficult to establish,

patients with a distant failure at the time of death would be censored as dying from cancer.

- Cardiac event free survival: the time from registration to cardiac event or death.
- Cardiac death: the time from registration to death due to cardiac reasons. Cardiac death would include documented congestive heart failure, myocardial infarction, arrhythmia*, heart block*, or any other cardiac cause documented in the medical records, death certificate, or autopsy as one of the major contributing causes of death.

  *Any lethal electrophysiologic change documented by the ICD before death would also be included.
- Overall survival: the time from registration to death due to any cause.

16.323 Adverse events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

Analyses for secondary endpoints will be descriptive in nature. Adjustment for multiple comparisons for the secondary analyses will not be done due to the exploratory nature of this research. Statistical tests on endpoints (t-test for continuous data; Wilcoxon rank-sum test, Fisher's exact test, or Chi-square test for ordinal data) will be utilized to determine differences at any particular time point. Graphical displays will be produced, such as mean profile plots or bar charts. Descriptive statistics of frequency (percentage) will be used to summarize AE incidence and severity as measured by the CTCAE 5.0. 95% confidence intervals will be constructed around point estimates.

16.33 Exploratory Endpoints

16.331 Imaging Changes: Imaging changes in the heart substructures associated with occurrence of cardiac events will be an exploratory component of this trial. Changes will be described at each time point using frequency distributions.

16.4 Data & Safety Monitoring:

16.41 Safety review

The principal investigator(s) and the study statistician will review the study monthly to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least biannually, based on reports provided by the MCCC Statistical Office.

16.41 Adverse Event Stopping Rules: The stopping rules specified below are based on the knowledge available at study development. The stopping rule applies to the overall study. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.
Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as “possible”, “probable”, or “definite”) that satisfy the following:

Adverse Events stopping rule

More than 3 patients with at least one grade 3 adverse events in the first 10 patients related or likely related to the cardiac monitor device would be used as a stopping rule for our observation protocol. We note that we will review grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously

unrecognized treatment-related adverse event. If at any point after the first 10 patients we see more than 30% of patients experiencing attributable grade 3 or higher adverse events then the study may be stopped at the investigator's discretion.

16.5 Results Reporting on ClinicalTrials.gov

At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints (i.e., "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 36 months after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the last patient registered has completed treatment.

16.6 Inclusion of Women and Minorities

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

16.62 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses. Inclusion based on minorities and gender will represent current patient demographics of patients treated at our institution. However, children under 18-years of age will be excluded because cardiac complications in the pediatric population are different than in adults.

16.63 The geographical region served by this study, has a population which includes approximately 5% minorities and 50% women. Based on prior MMC studies involving similar disease sites, we expect about 5% of patients will be classified as minorities by race and about 50% of patients

will be women. Expected sizes of racial by gender subsets for patients registered to this study are shown in the following table:

Ethnic Category	Sex/Gender			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	1	1	0	2
Not Hispanic or Latino	11	11	0	22
Ethnic Category: Total of all subjects*	12	12	0	**24**
Racial Category				
American Indian or Alaska Native	0	0	0	0
Asian	1	0	0	1
Black or African American	0	1	0	1
Native Hawaiian or other Pacific Islander	0	0	0	0
White	11	11	0	22
Racial Category: Total of all subjects*	12	12	0	**24**

Ethnic Categories: **Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”

Not Hispanic or Latino

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

None

18.0 Records and Data Collection Procedures

18.1 CRF Completion

This study will use Medidata Rave for remote data capture (RDC) of all study data. Forms should be submitted within 2 weeks of the visit occurring.

19.0 Budget

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded: cost of insertable cardiac monitor, impant/explant, biobanking, cardiac MRI, dried blood spot

20.0 References

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Mayo AZ procedures manual would be reviewed by the Radiation research committee and the specific Disease site group at Mayo AZ. UMC procedures manual would be also reviewed by the research committee and disease site groups at Mayo AZ. Alternatively, procedures manual elaborated at Mayo AZ can be incorporated into the UCM.

Appendix I ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

*As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From http://www.ecog.org/general/perf_stat.html