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Hypofractionated radiotherapy to the stellate ganglia for ventricular arrhythmia

Submission date 06/06/2024	**Recruitment status** Recruiting	[ ] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [X] Record updated in last year
Registration date 26/06/2024	**Overall study status** Ongoing	
Last Edited 10/10/2024	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims
Life threatening heart rhythms are often triggered by groups of nerves that speed up the heart. For patients at high risk of these dangerous rhythms implantable cardioverter defibrillators (ICD) can prevent death by terminating such rhythms, however they cannot prevent them from occurring in the first place. Despite all currently available medical therapy many patients experience recurrent dangerous rhythms and recurrent ICD shocks, leading to worse outcomes and significant impact on quality of life. Surgically removing the nerves that trigger these dangerous rhythms is a proven treatment for such patients. However the risk of complications from such a surgery is high. Image-guided hypofractionated radiotherapy has improved the precision and accuracy of radiation treatment for cancer to submillimetre levels . This new technology offers the ability to precisely target and modify the nerves going to the heart in a step wise manner without the risk of complications associated with surgery. This could potentially revolutionise treatment for patients who suffer from recurrent dangerous heart rhythms. We propose a study to establish the feasibility and safety of this approach.

Who can participate?
Only adult patients (over 18 years of age) with structural heart disease can participate in this study. Patients must have MRI safe implantable cardioverter defibrillator (ICD) devices and have experienced two or more appropriate ICD therapies in the preceding 6 months.

What does the study involve?
Participation will involve 9 study visits over the course of 9 months. Participants will undergo baseline MRI and CT scans of their stellate ganglia to enable planning of their radiotherapy treatment, and then proceed to Image-guided hypofractionated radiotherapy to their stellate ganglia. They will subsequently be followed up for 6 months post radiotherapy. Follow up will be in the form of study visits with the research team and remote monitoring of their ICD device, through their routine clinical care team. Follow up visits will include physical examination, ECG, bloods tests and completion of questionnaires. During the final study visit participants will also have a final MRI scan of their stellate ganglia.

What are the possible benefits and risks of participating?
There is a possibility that the radiotherapy treatment in this trial will reduce dangerous heart

rhythms, but it is likely that there will be no direct benefits from participating in the study. However, the information we gain from this study may help pave the way for a new treatments to prevent dangerous heart rhythms

Where is the study run from?
The study is run through the department of physiology, anatomy and genetics at the University of Oxford (UK)

When is the study starting and how long is it expected to run for?
May 2021 to May 2028

Who is funding the study?
British Heart Foundation (UK)

Who is the main contact?
Professor Neil Herring, neil.herring@dpag.oc.ac.uk

Contact information

Type(s)
Scientific

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Type(s)
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
327283

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 56907, FS/CRTF/22/24437, IRAS 327283

Study information

Scientific Title
Hypofractionated RADIOtherapy to the STellate ganglia for ventricular ARrhythmia

Acronym
RADIO-STAR

Study objectives
Current study hypothesis as of 10/10/2024:
Cardiac sympathetic denervation can be achieved non-invasively through Image-guided hypofractionated radiotherapy to the stellate ganglia, with minimal treatment-related adverse effects.

Previous study hypothesis:
Cardiac sympathetic denervation can be achieved non-invasively through MR-guided radiotherapy to the stellate ganglia, with minimal treatment-related adverse effects.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 02/02/2024, South Central - Oxford B Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8019; oxfordb.rec@hra.nhs.uk), ref: 24/SC/0005

Study design
Interventional non-randomized

Primary study design

Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See study outputs table

Health condition(s) or problem(s) studied
Arrhythmia

Interventions
Current interventions as of 10/10/2024:
Participation will involve a total of 9 visits over the course of 9 months. This includes the initial screening and planning scans, a full course of Image-guided hypofractionated radiotherapy and 6 months follow-up after completion of radiotherapy.

The first study visit is a screening visit at the John Radcliffe Hospital. Here the study procedures are discussed, and a screening consent is obtained from participants. At this visit a baseline cardiovascular examination is performed and baseline blood tests will be taken. Patients will be given a questionnaire to assess their baseline quality of life. We will review patients' ICD data to establish arrhythmia burden over the preceding 6 months and baseline heart rate characteristics. On this visit, all participants will undergo a screening MRI scan at OCMR to assess for imaging artefact and ability to tolerate MRI scanning. If this is successful they will then be invited to formally enter the study. If the results of the screening visit indicate patients are not eligible or safe to continue with our study, they will exit at this point.

The next study visit will be at a radiotherapy facility in Oxford. During this visit participants will meet the radiotherapy team who will be planning and carrying out their radiotherapy treatment. During this visit participants will be counselled about what to expect from their radiotherapy treatment and possible side effects. If patients are still willing to continue with the study informed written consent will be obtained for patients to formally enter the study.
Importantly all relevant risks would already have been covered in the initial screening consent. However, we still feel a dedicated visit with the radiotherapy team is important, to ensure patients have fully understood the process and any potential risks involved before formally entering the study. We have allocated a separate visit for this to allow patients a further opportunity to address questions relating to the radiotherapy process.

Once formally enrolled into this study planning for their radiotherapy treatment will begin. This will involve a further visit at the radiotherapy facility in Oxford for planning scans; a further MRI scan on the dedicated radiotherapy machine and a planning Computed Tomography (CT) scan. The purpose of these scans is to individually tailor radiotherapy sessions to allow us to accurately target the stellate ganglia in each patient. During this visit patients will have a bespoke mask fitted to their neck and shoulders which will be used during radiotherapy to accurately position patients in the radiotherapy machine.

Each patient will receive three fractions of Image-guided hypofractionated radiotherapy to the stellate ganglia, on alternate days over the course of 1 week. The total dose of radiotherapy received will be determined by our dose escalation protocol. This protocol is designed to allow us to safely and gradually increase the dose of radiotherapy over the course of the study, until we find a dose that is both safe and effective at modifying the stellate ganglia. We will follow a dose escalation protocol to determine the lowest radiotherapy dose that can safely achieve sympathetic downregulation. The first 3 patients would be treated at 8 Gy per fraction for 3 fractions on alternate days, with the aim of increasing to 9 Gy per fraction for 3 fractions on alternate days in another 3 patients, 10 Gy per fraction for the next 3 patients for 3 fractions on alternate days and 11 Gy per fraction for 3 fractions on alternate days for the final 4 patients.

There will be a minimum of 6 weeks between the last participant treated at each dose before escalation to the next dose to allow for the detection of adverse events at the participants' 6-week follow-up visit. Before each dose escalation we will have an independent safety committee review all patient data and radiotherapy doses will only be escalated if there are no safety concerns.

Prior to each fraction of radiotherapy blood samples (approximately 16 ml) will be taken to measure biomarker levels. Routine blood tests (including renal function, full blood count and thyroid function) will also be checked prior to the first fraction of treatment.

Before and after each fraction of radiotherapy a cardiovascular examination and neurological examination will be performed by one of the study doctors paying close attention to signs of any side effects from the treatment. Cardiovascular observations including postural blood pressures and heart rate will be recorded, and an electrocardiogram will be performed. If any serious treatment-related adverse events are detected, then no further fractions of radiation will be delivered to that patient.

Over the course of 6 months post-completion of Image-guided hypofractionated radiotherapy patients will be followed up to monitor for treatment-related adverse events and determine the effectiveness of our treatment. This will comprise of three further study visits, at the John Radcliffe Hospital, at 6 weeks, 3 months and 6 months (or earlier if clinically indicated) following completion of radiotherapy. During each study visits blood samples will be taken, physical examinations and observations will be performed, an electrocardiogram will be taken and patients will be asked to complete a questionnaire. At the final 6-month visit a 1.5T MRI scan will also be repeated at the OCMR to reassess cardiac function and stellate ganglion anatomy.

Previous interventons:
Participation will involve a total of 9 visits over the course of 9 months. This includes the initial screening and planning scans, a full course of MRI-guided radiotherapy and 6 months follow-up after completion of radiotherapy.

The first study visit is a screening visit at the John Radcliffe Hospital. Here the study procedures are discussed, and a screening consent is obtained from participants. At this visit a baseline cardiovascular examination is performed and baseline blood tests will be taken. Patients will be given a questionnaire to assess their baseline quality of life. We will review patients' ICD data to establish arrhythmia burden over the preceding 6 months and baseline heart rate characteristics. On this visit, all participants will undergo a screening MRI scan at OCMR to assess for imaging artefact and ability to tolerate MRI scanning. If this is successful they will then be invited to formally enter the study. If the results of the screening visit indicate patients are not eligible or safe to continue with our study, they will exit at this point.

The next study visit will be at the GenesisCare facility in Oxford. During this visit participants will meet the radiotherapy team who will be planning and carrying out their radiotherapy treatment. During this visit participants will be counseled about what to expect from their radiotherapy treatment and possible side effects. If patients are still willing to continue with the study informed written consent will be obtained for patients to formally enter the study. Importantly all relevant risks would already have been covered in the initial screening consent. However, we still feel a dedicated visit with the radiotherapy team is important, to ensure patients have fully understood the process and any potential risks involved before formally entering the study. We have allocated a separate visit for this to allow patients a further opportunity to address questions relating to the radiotherapy process.

Once formally enrolled into this study planning for their radiotherapy treatment will begin. This will involve a further visit at the GenesisCare facility in Oxford for planning scans; a further MRI scan on the dedicated radiotherapy machine and a planning Computed Tomography (CT) scan. The purpose of these scans is to individually tailor radiotherapy sessions to allow us to accurately target the stellate ganglia in each patient. During this visit patients will have a bespoke mask fitted to their neck and shoulders which will be used during radiotherapy to accurately position patients in the radiotherapy machine.

Each patient will receive three fractions of MRI-guided radiotherapy to the stellate ganglia, on alternate days over the course of 1 week, at the GenesisCare facility in Oxford. The total dose of radiotherapy received will be determined by our dose escalation protocol. This protocol is designed to allow us to safely and gradually increase the dose of radiotherapy over the course of the study until we find a dose that is both safe and effective at modifying the stellate ganglia. We will follow a dose escalation protocol to determine the lowest radiotherapy dose that can safely achieve sympathetic downregulation. The first 3 patients would be treated at 8 Gy per fraction for 3 fractions on alternate days, with the aim of increasing to 9 Gy per fraction for 3 fractions on alternate days in another 3 patients, 10 Gy per fraction for the next 3 patients for 3 fractions on alternate days and 11 Gy per fraction for 3 fractions on alternate days for the final 4 patients.

There will be a minimum of 6 weeks between the last participant treated at each dose before escalation to the next dose to allow for the detection of adverse events at the participants' 6-week follow-up visit. Before each dose escalation we will have an independent safety committee review all patient data and radiotherapy doses will only be escalated if there are no safety concerns.

Prior to each fraction of radiotherapy blood samples (approximately 16 ml) will be taken to measure biomarker levels. Routine blood tests (including renal function, full blood count and thyroid function) will also be checked prior to the first fraction of treatment.

Before and after each fraction of radiotherapy a cardiovascular examination and neurological examination will be performed by one of the study doctors paying close attention to signs of any side effects from the treatment. Cardiovascular observations including postural blood pressures and heart rate will be recorded, and an electrocardiogram will be performed. If any serious treatment-related adverse events are detected, then no further fractions of radiation will be delivered to that patient.

Over the course of 6 months post-completion of MRI-guided radiotherapy patients will be followed up to monitor for treatment-related adverse events and determine the effectiveness of our treatment. This will comprise of three further study visits, at the John Radcliffe Hospital, at 6 weeks, 3 months and 6 months (or earlier if clinically indicated) following completion of

radiotherapy. During each study visits blood samples will be taken, physical examinations and observations will be performed, an electrocardiogram will be taken and patients will be asked to complete a questionnaire. At the final 6-month visit a 1.5T MRI scan will also be repeated at the OCMR to reassess cardiac function and stellate ganglion anatomy.

Intervention Type
Other

Primary outcome measure
Current primary outcome measures as of 10/10/2024:
During all Image-guided hypofractionated radiotherapy sessions and monitoring visits up to 6 months post radiotherapy:
1. Treatment-related serious adverse events (SAEs) defined as any grade 3 toxicity requiring hospitalization or any grade 4 to 5 toxicity as defined by the common terminology criteria for adverse events
2. Treatment-related side effects based on patient symptom questionnaires and clinical examination during study visits

Previous primary outcome measures:
During all MR-guided radiotherapy sessions and monitoring visits up to 6 months post radiotherapy:
1. Treatment-related serious adverse events (SAEs) defined as any grade 3 toxicity requiring hospitalization or any grade 4 to 5 toxicity as defined by the common terminology criteria for adverse events
2. Treatment-related side effects based on patient symptom questionnaires and clinical examination during study visits

Secondary outcome measures
Current secondary outcome measures as of 10/10/2024:
1. Assess the feasibility of Image-guided hypofractionated radiotherapy to modify the stellate ganglia to achieve anatomical and functional sympathetic denervation.
This will be assessed according to the following outcome measures:
1.1. Physical modification of the stellate ganglia on MRI at baseline and at 6 months
1.2. Heart rate variability at baseline and at 6 months
1.3. Peripheral venous biomarker concentrations (Neuropeptide-Y, and catecholamines) at baseline and at 6 months.
1.4. The number of ventricular arrhythmias requiring device therapy 6 months before and after radiotherapy
1.5. Patient-reported outcomes assessed with the KCCQ-23 questionnaire at baseline and at 6 months.
2. Correlate the change in circulating biomarker levels with the efficacy of Image-guided hypofractionated radiotherapy to modify the stellate ganglia in terms of arrhythmic burden. This will be assessed through statistical correlation between changes in measured biomarker concentrations and changes in the number of ventricular arrhythmias.

Previous secondary outcome measures:
1. Assess the feasibility of MR-guided radiotherapy to modify the stellate ganglia to achieve anatomical and functional sympathetic denervation.
This will be assessed according to the following outcome measures:
1.1. Physical modification of the stellate ganglia on MRI at baseline and at 6 months
1.2. Heart rate variability at baseline and at 6 months

1.3. Peripheral venous biomarker concentrations (Neuropeptide-Y, and catecholamines) at baseline and at 6 months.
1.4. The number of ventricular arrhythmias requiring device therapy 6 months before and after radiotherapy
1.5. Patient-reported outcomes assessed with the KCCQ-23 questionnaire at baseline and at 6 months.
2. Correlate the change in circulating biomarker levels with the efficacy of MR-guided radiotherapy to modify the stellate ganglia in terms of arrhythmic burden. This will be assessed through statistical correlation between changes in measured biomarker concentrations and changes in the number of ventricular arrhythmias.

Overall study start date
01/05/2021

Completion date
01/05/2028

Eligibility

Key inclusion criteria
1. Male or Female, aged at least 18 years old.
2. Known diagnosis of structural heart disease defined as any patient with impaired left ventricular ejection fraction (less than 55%) due to any cause including; ischaemic cardiomyopathy, dilated cardiomyopathy, hypertrophic cardiomyopathy or Arrhythmogenic cardiomyopathy.
3. CMR compatible ICD device implanted a minimum of 6 months ago, under follow-up at Oxford University Hospitals NHS Foundation Trust.
4. Experienced more than one appropriate ICD therapy (shocks or anti-tachycardia pacing) for ventricular arrhythmia in the last 6 months
5. Established on optimal guideline-based medical therapy for heart failure

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 13; UK Sample Size: 13

Key exclusion criteria
General Exclusion Criteria:
1. Device radiation dose or nearby organs at risk exceeding the limit for low-risk radiotherapy as defined by the UK Consensus and AAPM 2019 guidelines

2. Female patients who are pregnant, lactating or planning pregnancy during the study period
3. Patients who are terminally ill, inappropriate for intervention, or unable to consent
4. Any impediment to communication which, in the opinion of the investigator, might prevent the investigator communicating effectively with the patient during the study which could cause a safety or reliability concern.
5. Any other condition which, in the opinion of the investigator, might affect the safety of the participant or reduce the reliability of the study results
6. Involvement in any other research project where the procedures would affect the outcomes of this study.

Additional Exclusion Criteria for Participants Undergoing MRI Studies:
7. Metal clips or metallic foreign body
8. Prior injury to the eye involving fragments of metal
9. Prior shrapnel injuries
10. Any other metallic or electronic implants affected by the magnetic field
11. History of severe claustrophobia
12. Severe liver damage, TB, pulmonary disease, anaemia, blood coagulation disorders

Date of first enrolment
01/05/2024

Date of final enrolment
01/05/2027

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
John Radcliffe Hospital
Headley Way
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Sponsor information

Organisation
University of Oxford

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Sponsor type
University/education

Website
http://www.ox.ac.uk/

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation

Alternative Name(s)
the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a peer-reviewed journal

Intention to publish date
01/05/2029

Individual participant data (IPD) sharing plan

A fully anonymised version of the dataset used for analysis with individual participant data and will be available for other researchers to apply to use 1 year after publication. Written proposals (submitted to Professor Neil Herring) will be assessed by members of the trial team and a decision made about the appropriateness of the use of data. A data-sharing agreement will be put in place before any data are shared.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 1.1	23/01/2024	21/06/2024	No	Yes