



BMJ Open Protocol of the RADIO-STAR trial: a phase 1 safety and dose finding study of hypofractionated radiotherapy to the stellate ganglia for the treatment of ventricular arrhythmia

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ABSTRACT

Introduction Sympathetic activation is the hallmark of cardiac disease, driving disease progression and triggering ventricular arrhythmia (VA). Despite optimal medical therapy, many patients experience recurrent VAs refractory to medical therapy, leading to repetitive implantable cardioverter defibrillator (ICD) therapy, worse quality of life and adverse outcomes. Cardiac sympathetic denervation (CSD) through surgical removal of the stellate ganglia is an effective treatment for refractory VAs but carries a high complication rate. We hypothesise that high precision image guided radiotherapy can be used to target the stellate ganglia to achieve CSD non-invasively.

Methods and analysis RADIO-STAR (hypofractionated radiotherapy to the stellate ganglia for ventricular arrhythmia) is a first-in-human, phase 1 safety and dose finding study of radiotherapy to the stellate ganglia in patients with recurrent VAs. Patients with structural heart disease requiring recurrent ICD therapy for VAs are invited to undergo radiotherapy bilaterally to their stellate ganglia with a predetermined sample size of n=13. Radiotherapy dose will be determined by a prespecified dose escalation protocol. The primary outcome is safety defined as any treatment-related grade 3–5 toxicity occurring within 6 months of radiotherapy treatment, as defined by the Common Terminology Criteria for Adverse Events or any treatment-related side effects detected on patient symptom questionnaires and clinical examination during study visits. Secondary outcome measures to evaluate feasibility and efficacy include ability to safely deliver radiotherapy and consequent changes in circulating catecholamines and neuropeptide-Y, heart rate variability, structural changes in the stellate ganglia on MRI imaging and ICD therapy burden.

Ethics and dissemination This study has received ethical approval by the South Central—Oxford B Research Ethics Committee (REC/SC/0005). Study findings will be submitted for publication in peer-reviewed scientific journals and presented at national and/or international scientific conferences.

Trial registration number [ISRCTN49861434](https://www.clinicaltrials.gov/ct2/show/study/NCT049861434).

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This first-in-human study will establish the safety and feasibility of radiotherapy to the stellate ganglia and provide key data on radiotherapy dose selection for future randomised controlled trials evaluating the efficacy and durability of radiotherapy-induced cardiac sympathetic denervation for the prevention of ventricular arrhythmia.
- ⇒ As an early-phase, safety-focused investigation, this study is not powered to assess clinical efficacy, so the evaluation of treatment effects on arrhythmia burden is beyond the scope of this study.
- ⇒ In the absence of a control group, changes in implantable cardioverter defibrillator (ICD) therapy burden following radiotherapy may be confounded by concurrent clinical interventions, including ventricular tachycardia ablation, adjustments to antiarrhythmic medications or reprogramming of ICD settings, and should be interpreted with caution.
- ⇒ The maximum follow-up period of 6 months limits assessment of long-term outcomes but is sufficient for initial safety assessment and radiotherapy dose evaluation.
- ⇒ Observed changes in heart rate variability, circulating biomarkers or stellate ganglion appearance on MRI represent indirect evidence of reduced cardiac sympathetic tone and should be interpreted as hypothesis-generating only.

INTRODUCTION

Ventricular arrhythmias (VA) are life-threatening events and the most common cause of sudden cardiac death (SCD).¹ SCD accounts for up to 20% of deaths in the western world.² Patients with structural heart disease such as heart failure with reduced ejection fraction (HFrEF) are at particularly increased risk of SCD. There are approximately 6.7 million Americans living with heart failure, and 1 in 4 are expected to develop



heart failure within their lifetime.³ While advances in medical therapy have improved outcomes in HFrEF, the incidence of SCD remains stubbornly high.⁴

In patients at very high risk of SCD, the implantable cardioverter defibrillator (ICD) improves mortality.^{5 6} While ICDs are effective at treating VAs as they occur, and thus reducing mortality associated with SCD, they cannot prevent VAs from occurring in the first place. Patients with incessant VAs thus experience recurrent ICD therapies associated with increased mortality⁷ and significant impact on quality of life.^{8 9} Prevention of VAs is thus vital.

β -blockers are the only class of antiarrhythmic medication that reduce mortality due to VAs in heart failure.^{10 11} While other classes of antiarrhythmic drugs can reduce VAs, they lack a mortality benefit,^{5 12 13} are associated with side effects^{14 15} and can even lead to excess mortality through proarrhythmic effects.^{16–18} Catheter ablation can be effective at reducing VAs,¹⁹ but up to a third of patients have recurrence of VAs, and clinical trials of VT ablation have to-date failed to demonstrate a mortality benefit.^{20–24} Thus, despite all contemporary treatments, the incidence of arrhythmia and death in patients with HFrEF remains high, at around 5–10% per year.^{5 6 25 26} For such patients few remaining options exist. Heart transplantation may also be considered but is limited by organ availability and stringent candidate selection criteria.²⁷

The heart is densely innervated by a network of autonomic neurons^{28 29} which control every aspect of cardiac function including electrophysiological properties of cardiac tissue.^{30–34} Conceptually, the autonomic nervous system can be considered to exert its influence through two opposing arms; the sympathetic system which increases inotropy, chronotropy, lusiotropy and dromotropy, and the parasympathetic system which decreases these parameters.^{35 36} In health, this system exists in a state of intricate balance to maintain cardiac homeostasis.³⁷ However, the hallmark of cardiac failure, irrespective of aetiology, is a loss of this balance resulting in sympathetic activation and parasympathetic withdrawal.^{38 39} While initially, sympathetic activation preserves cardiac output in response to acute cardiac insult, over time it becomes maladaptive and contributes to disease progression.^{40 41}

Sympathetic tone is highly proarrhythmic. β -adrenergic stimulation alters cardiomyocyte repolarisation through protein kinase A and calcium/calmodulin-dependent protein kinase II mediated phosphorylation of calcium handling proteins and ion channels. Activation of L-type calcium channels, the ryanodine receptor 2, sodium/calcium exchange and smooth endoplasmic reticulum calcium ATPase leads to calcium loading in cardiomyocytes.⁴² Calcium loading predisposes to delayed afterdepolarisations which are triggers for many pathological arrhythmias.^{32 43 44} Furthermore, by increasing the slow outward potassium current, β -adrenergic stimulation shortens action potential duration (APD),⁴⁵ which decreases refractory period and helps sustain re-entry circuits that underlie most VAs.

Recently, the importance of sympathetic cotransmitters such as neuropeptide-Y (NPY) has also been established. Notably, NPY has strong proarrhythmic effects even in the presence of maximal β -blockade^{46 47} mediated by ventricular myocyte Y1 receptor promotion of calcium signalling. In fact, NPY may serve as a potential biomarker of arrhythmic risk and has been shown to predict arrhythmia and death in chronic heart failure and following myocardial infarction.^{46 48 49}

The majority of cardiac sympathetic innervation arises from the stellate ganglia; a fusion of the lower cervical and first thoracic sympathetic ganglia.^{50 51} In vivo, stimulation of the stellate ganglia decreases fibrillatory threshold and induces VA.^{34 52–54} Additionally, regional differences in cardiac sympathetic innervation produce regional heterogeneity in cardiac myocyte electrical properties which predisposes to arrhythmia.^{55–58} Indeed, stellate ganglion stimulation increases the time interval from the peak to the end of the electrocardiographic T wave, a marker of cardiac dispersion of repolarisation and an independent predictor for risk of SCD.³³ In ischaemic heart disease, these effects are further compounded by sympathetic nerve sprouting at infarct border zones, super sensitivity in infarcted myocardium⁵⁹ and differing responses to sympathetic stimulation in ischaemic versus normal myocardium, enhancing regional differences in ventricular refractoriness and predisposing to arrhythmia.⁶⁰ Heterogeneity in APD and activation-recovery intervals is further amplified by sympathetic stimulation of the sinoatrial node, which through increases in heart rate promotes discordant calcium-driven APD alternans.⁶¹

Finally, sympathetic activation inhibits parasympathetic tone through sympathovagal crosstalk, further entrenching autonomic imbalance and limiting the cardioprotective and antiarrhythmic effects of parasympathetic activation.^{62–68}

Unsurprisingly, methods to reduce sympathetic tone have emerged as promising treatments for VAs. Deep sedation is known to reduce overall sympathetic tone and is effective during arrhythmic storm.⁶⁹ Similarly, injection of local anaesthetic into the epidural space at level T1–T4 where cardiac sympathetic preganglionic fibres emerge (called thoracic epidural anaesthesia) or direct stellate ganglion block can be used to manage arrhythmic storm.^{70–73} While these techniques are effective holding measures, a more permanent form of cardiac sympathetic denervation (CSD) can be achieved through surgical removal of the lower half of the stellate ganglia along with T2–T4 sympathetic ganglia.^{74–76}

In the 1990s, Schwartz and colleagues pioneered surgical CSD as a treatment for patients at high arrhythmic risk due to long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardias (CPVTs). They showed that patients with recurrent cardiac arrest despite maximal β -blocker therapy could be successfully treated with CSD.^{77–79} This led to widespread adoption of surgical CSD^{80–83} and its inclusion in clinical guidelines for managing patients with LQTS and CPVT.⁸⁴ Schwartz

*et al*⁸⁵ also demonstrated the utility of CSD in ischaemic heart disease. In a small randomised trial, 144 patients with MI complicated by VAs were randomised to placebo, CSD or β -blockers. Over a 22-month follow-up the rate of SCD (21%) in the control group was markedly reduced by both β -blockade and SCD (2.7% and 3.6%, respectively).

However, the use of CSD in HFrEF initially remained limited due to concerns regarding haemodynamic decompensation resulting from removal of sympathetic drive. However, Shivkumar¹⁹ and colleagues have since dispelled these concerns. They showed that CSD is safe in the presence of HFrEF and that bilateral surgical CSD is more effective at preventing VAs than left-only CSD.^{58 74 86} Indeed, bilateral CSD is strikingly effective, leading to over 60% reduction in VAs in patients refractory to all available treatments, including maximally tolerated doses of β -blockade.⁸⁷ Unfortunately, despite progressive refinements of surgical SCD, including minimally invasive video-assisted thoracoscopic approaches,⁸³ the procedure continues to carry high complication rates, limiting its mainstream use.^{87 88} Furthermore, surgery requires long hospital stays often including postoperative intensive care admissions.⁸⁹

Modern image-guided radiotherapy can deliver highly targeted treatments with submillimetre precision and steep dose gradients, allowing for rapid dose fall-off outside the treatment area. This has revolutionised cancer treatment by enabling the safe delivery of high-dose radiotherapy to small tumours while still minimising radiation dose to surrounding healthy tissues.^{90–92} We hypothesise that this technology could be used to target the stellate ganglia to achieve CSD non-invasively, resulting in fewer complications while maintaining efficacy.

METHODS AND ANALYSIS

This protocol is reported in accordance with the Standard Protocol Item Recommendations for Interventional Trials 2025 guidance⁹³ (online supplemental file 2).

Study design

RADIO-STAR (hypofractionated radiotherapy to the stellate ganglia for ventricular arrhythmia) is a phase 1 clinical trial to evaluate the safety, feasibility and optimal dose of image guided radiotherapy to the stellate ganglia to achieve CSD. The study comprises a multidisciplinary team including oncologists, neuroradiologists and cardiologists. The overall study design is illustrated in figure 1, and the full trial protocol is available as an online supplement (Data online supplemental file 2)

All participants will receive radiotherapy bilaterally to the lower half of their stellate and T1–2 sympathetic ganglia. Evidence suggests that the risk of Horner's syndrome and hyperalgesia may be mitigated by sparing the cranial portion of the stellate ganglion and the T3–T4 paravertebral ganglia while still achieving sufficient CSD.^{51 74 76} Radiotherapy will be delivered in three fractions from a total starting dose of 24Gy (the maximum upper limit for radiation dose to neuronal structures such as the brachial plexus),⁹⁴ to a maximum dose of 33 Gy. Radiotherapy doses are derived from historical literature targeting other neuronal structures such as the trigeminal ganglia.^{95–100} The 'neurosurgical approach' involving very large single-fraction doses of up to 90 Gy, as commonly used to treat trigeminal neuralgia,¹⁰¹ is likely to be higher than required. Rather, lower subablative doses to achieve functional ganglion modification instead of its destruction may be adequate.¹⁰² Furthermore, this would reduce

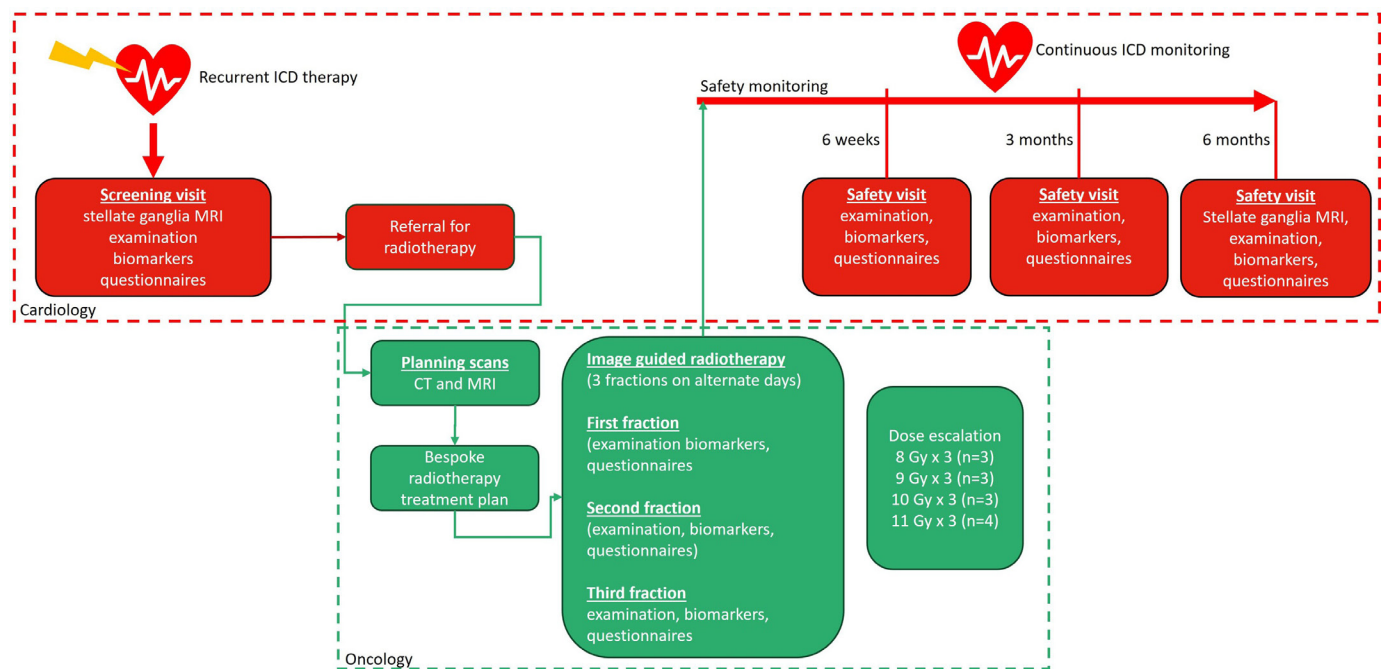


Figure 1 Flow diagram illustrating overall study design of the RADIO-STAR trial. ICD, implantable cardioverter defibrillator; RADIO-STAR, hypofractionated radiotherapy to the stellate ganglia for ventricular arrhythmia.

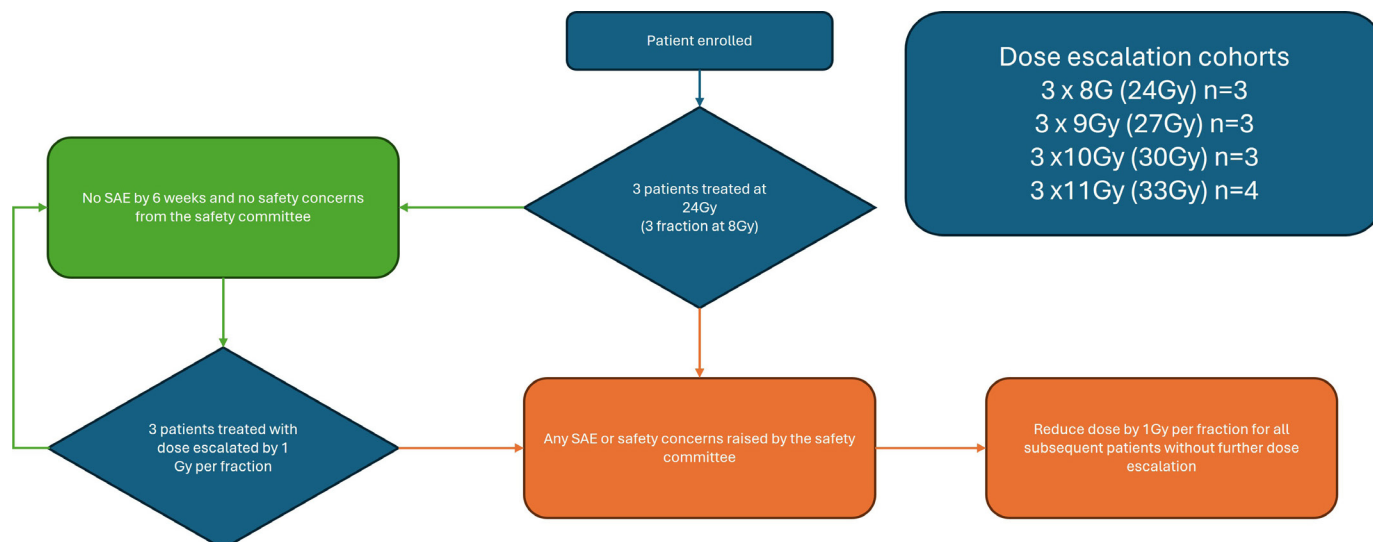


Figure 2 Dose escalation protocol. The first three participants will be treated at a total dose of 24 Gy as 8 Gy per fraction for three fractions on alternate days. If no related SAEs occur in this cohort, the dose will be escalated by 1 Gy per fraction for the subsequent three patients. This will be repeated up to a maximum dose of 11 Gy per fractions (total 33 Gy) for the final four patients. There will be a minimum of 6 weeks between the last participant treated at each dose before escalating the next dose to allow for detection of adverse events at participants' 6 week follow-up visit. Before each dose escalation, an independent safety committee will review all patient data and radiotherapy doses will only be escalated if there are no safety concerns. In the event of a related SAE, no further fractions would be given to that patient, and the dose would be reduced by 1 Gy per fraction for all subsequent patients (up to a total of 13 patients) without further dose escalation. An early stopping rule will be set to halt enrolment if four out of the first eight patients develop a related SAE. SAEs in this trial are defined as any Grade 5, Grade 4 or Grade 3 toxicity requiring hospitalisation as defined by the Common Terminology Criteria for Adverse Events (V.5.0). SAE, serious adverse event.

the risk of off-site neurological sequelae and minimise radiation dose to nearby organs at risk (OAR) and ICD devices. Radiotherapy will be delivered under either CT (Varian TrueBeam) or MRI (MRIdian MR-Linac) image guidance. Treatment dose will be prespecified by an 'up-and-down' dose escalation protocol^{103 104} designed to identify the maximum tolerated radiotherapy dose (figure 2).

Objectives

The primary objective of this study is to determine if image-guided radiotherapy to the stellate ganglia is feasible and safe.

Patient population

This study aims to recruit thirteen patients with structural heart disease who experience recurrent VAs requiring ICD therapy despite optimised medical treatment. Patients receiving care at the John Radcliffe Hospital, Oxford, UK, who meet the eligibility criteria (see box 1) will be considered.

Study plan

Participation in this study will consist of nine visits, including an initial screening visit, followed by eight study visits over the course of approximately 6 months (figure 1). A schedule of events of all study procedures is available as part of the full trial protocol on-line (data online supplemental file 2).

Visit 1: screening visit and screening 1.5T MRI

Participants will be asked to provide written informed consent prior to screening. Patient age, height, weight, gender, prior diagnosed comorbidities, cardiac function, smoking status, Canadian Cardiovascular Society angina grade, New York Heart Association heart failure severity and medication history will be recorded. The Kansas City Cardiomyopathy Questionnaire (KCCQ-23) will assess baseline quality of life scores, and routine cardiovascular and neurological examination will establish baseline clinical status. A 12-lead ECG, 10 min heart rate variability (HRV) measurements, postural blood pressures and baseline blood tests will also be taken.

An MRI scan of the stellate ganglia will be performed to ensure adequate visualisation of the stellate ganglia. We have undertaken extensive pilot work to optimise T2-weighted turbo spin echo MRI sequences with short tau inversion recovery fat suppression to clearly visualise the stellate ganglia while minimising device-related artefact (figure 3). This imaging will be used for preliminary planning to evaluate whether the intended treatment dose can be delivered to the stellate ganglion without exceeding the maximum tolerated doses for the ICD device or adjacent OAR. If it is not possible to deliver radiotherapy without exceeding the limit for low-risk radiotherapy to OAR—as defined by the UK and American Association of Physicists in Medicine 2019 consensus^{94 105–107}—the patient will be withdrawn.

Box 1 Study inclusion and exclusion criteria

Inclusion criteria

- ⇒ Participant is willing and able to give informed consent for participation in the study.
- ⇒ Male or female, aged at least 18 years old.
- ⇒ 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.
- ⇒ MRI-compatible ICD device implanted a minimum of 6 months ago, under follow-up at Oxford University Hospitals NHS Foundation Trust.
- ⇒ Experienced more than one appropriate ICD therapy (shocks or ATP) for ventricular arrhythmia in the last 6 months.
- ⇒ Established on optimal guideline-based medical therapy for heart failure and ventricular arrhythmia.

Exclusion criteria

- ⇒ 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.
- ⇒ Severe kidney impairment (eGFR less than 30) which would prevent the safe use of iodine contrast during CT scans.
- ⇒ Female patients who are pregnant, lactating or planning pregnancy during the study period.
- ⇒ Patients who are terminally ill, inappropriate for intervention or unable to consent.
- ⇒ 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.
- ⇒ Any other condition which, in the opinion of the investigator, might affect the safety of the participant or reduce the reliability of the study result.
- ⇒ Involvement in any other research project where the procedures would affect the outcomes of this study.
- ⇒ Any condition preventing the safe use of MRI imaging (metal clips or metallic foreign body, prior injury to the eye involving fragments of metal, prior shrapnel injuries, any other metallic or electronic implants affected by the magnetic field, history of severe claustrophobia).

AAPM, American Association of Physicists in Medicine; ATP, Anti-Tachycardia Pacing; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator.

Visit 2: radiotherapy team visit and study consent

Only patients with adequate stellate ganglia visualisation and acceptable radiotherapy treatment plans will proceed with the study. This process will begin with an introductory visit to the radiotherapy team. Patients will receive detailed counselling about the radiotherapy procedure, potential side-effects and will be asked to provide written informed consent for full study enrolment.

Visit 3: planning scans, radiotherapy delineation and treatment planning

A planning contrast CT scan of the stellate ganglia necessary for further treatment planning will be performed. Participants receiving MR-guided radiotherapy will

also undergo an additional 0.35T MRI planning scan performed on the MRIdian MR-Linac. Both images will be fused with the pretreatment diagnostic MRI to aid organ contouring. Accurate positioning for the planning scan and subsequent treatment will be facilitated by a 5-point thermoplastic mask immobilising patient head and shoulders. Optimal fields of view for CT and MRI scans (if required) will be from the patient's inferior orbital ridges to carina. Imaging slice thickness will be 2 mm on CT and 1.5 mm on 0.35T MRI.

The stellate, T1 and T2 ganglia will be identified with the aid of the baseline 1.5T MR images coregistered with the CT and 0.35T MR planning images. The clinical target volumes (CTVs) are defined as the lower half of the stellate ganglion, T1 ganglion and T2 ganglion bilaterally (CTV-right and CTV-left). A planning target volume (PTV) will be created around each CTV with an additional 3 mm margin to account for any uncertainties in treatment planning and delivery (PTV-right, PTV-left). The prescription dose will be prescribed to this volume, such that 95% of the volume should receive 100% of the dose (see figure 4).

Dose distribution will be heterogeneous, with a moderately high maximum dose (up to 120%) at the centre of the PTV. Dose gradients will be steep outside of the PTVs to minimise dose to adjacent OAR. PTV coverage will be compromised to ensure adjacent OAR dose constraints are achieved (as shown in table 1).^{94 106 107} The minimum acceptable volume (V100%) coverage of PTV-right and PTV-left individually is 75%.

Visits 4–6: hypofractionated radiotherapy to the stellate ganglia

Radiotherapy will be delivered in three fractions on alternate days, over the course of 1 week. Before and after each fraction of radiotherapy, cardiovascular and neurological examinations, ECGs, HRV measurements, postural blood pressures and symptoms questionnaire scores will be recorded. A blood sample will be taken after each fraction. This gives the opportunity to pause radiotherapy delivery should side effects develop. Treatment will be delivered with daily image guidance, via bony anatomy adjacent to the PTV, adjustment of the couch position and matching of the treatment target to within the PTV. The position of the brachial plexus will also be monitored to confirm it remains within the OAR dose constraint.

Visits 7–9: safety visits

Study follow-up will comprise three study visits at 6 weeks, 3 months and 6 months following completion of radiotherapy. During each study visit, cardiovascular and neurological examinations, ECGs, HRV measurements, postural blood pressures and symptoms questionnaire scores will be recorded and a blood sample taken. At the final 6-month study visit, participants will also complete the KCCQ-23 and undergo a final stellate ganglion 1.5T MRI. As part of study follow-up, a record will be kept of

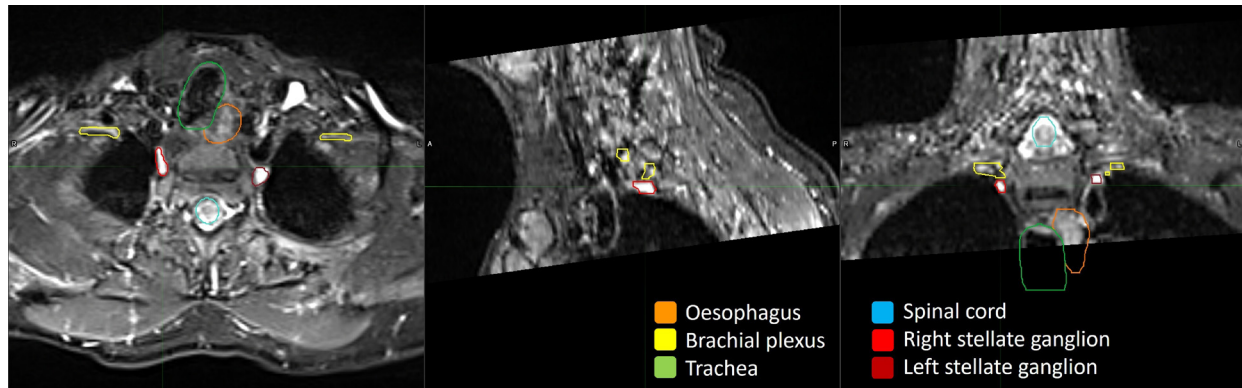


Figure 3 1.5T MRI diagnostic imaging of the stellate ganglia. A T2 weighted turbo spin echo MRI with short tau inverted recovery fat suppression of a participant with a left sided ICD device. Planning target volumes are contoured over the stellate ganglia and key dose-limiting organs. ICD, implantable cardioverter defibrillator.

patients' arrhythmia management by their usual clinical team including cardiac ablation procedures, changes in cardiac medications and alterations to ICD programming parameters.

ICD interrogation and monitoring

Throughout the study duration, all patients ICDs will be under remote monitoring as part of routine clinical care. In addition, ICDs will be interrogated at each study visit to screen for device-related complications resulting from radiotherapy.

Outcome measures

The primary outcome of this study is safety, and this study is powered to detect serious adverse events (SAE) as our primary endpoint. SAE is defined as any related and unexpected grade 3 toxicity requiring hospitalisation, grade 4 toxicity or grade 5 toxicity as defined by the Common Terminology Criteria for Adverse Events V.5.0. Relatedness of any SAE to the trial intervention will be decided by an independent safety committee. The presence of less severe treatment-related side effects will be assessed through a dedicated symptom questionnaire (data online supplemental file 3) and full cardiovascular and

neurological examination by a trained clinical member of the study team at every radiotherapy and follow-up visit. The symptom questionnaire includes a comprehensive list of symptoms that are commonly reported following surgical CSD^{88 108} and radiotherapy treatment for head and neck cancers.¹⁰⁹ Any radiotherapy-related side effects will be correlated with total radiation dose and biological effective dose to the relevant OAR.

Secondary outcome measures to assess efficacy include measuring radiotherapy-induced changes in circulating norepinephrine and NPY levels, ICD therapy burden, HRV and structural changes in the stellate ganglia detected on 1.5T MRI imaging (as shown in table 2). Finally, the effect on patient quality of life will be assessed by the KCCQ-23 which has been extensively validated to assess health status and quality of life in patients with a range of cardiomyopathies.¹¹⁰⁻¹¹³

Sample size calculation

This study is designed to ensure the SAE rate of radiotherapy to the stellate ganglia does not exceed 34%⁸⁷ as its primary outcome. We calculated sample size using the Wald approximation ensuring that the upper bound of

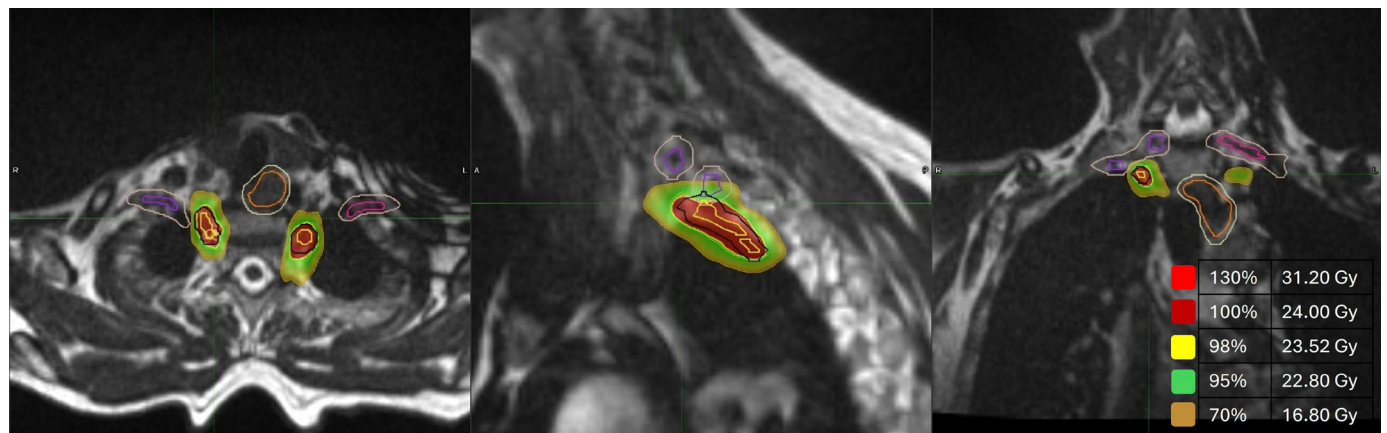


Figure 4 Radiotherapy doses displayed on the 0.35T TruFi planning image. Radiotherapy isodose lines over the stellate ganglia for a patient with target total dose of 24 Gy. Also displayed are the contours over the oesophagus (orange) and brachial plexus (purple) with a surrounding planning organ at risk volume.

Table 1 Dose constraints to organs at risk

Organ at risk	Metric	Total dose over three fractions
Brachial plexus	D(0.1 cc)	≤24.0 Gy
Chest wall	D(0.1 cc)	≤36.9 Gy
	D(30.0 cc)	≤30.0 Gy
Great vessels	D(0.1 cc)	≤45.0 Gy
Oesophagus	D(0.1 cc)	≤25.2 Gy
Lungs	V(20 Gy)	≤15%
Spinal cord	D(0.1 cc)	≤20.3 Gy
Skin	D(0.1 cc)	≤33.0 Gy
	D(10.0 cc)	≤30.0 Gy
Trachea	D(0.1 cc)	≤30.0 Gy
Carotid artery	D(0.03 cc)	≤32.5 Gy
Thyroid lamina	D(0.03 cc)	≤30.0 Gy
ICD generator	D (0.03 cc)	≤5.0 Gy

D(xx cc) <yy Gy denotes the maximum dose (yy Gy) that can be given to a specified volume of the organ (xx cc), with the remaining volume receiving less than the threshold dose. V(yy Gy) <xx% denotes the maximum critical percentage volume of the organ (xx %) that can receive the specified threshold dose (yy Gy). ICD, implantable cardioverter defibrillator.

the 95% CI (Confidence Interval) for observed adverse events would not exceed 34%. Assuming an observed SAE rate of 16% (by subtracting rates of surgical complications from overall complications rates associated with surgical CSD) we require 13 participants to ensure that the upper limit of the 95% CI around the observed SAE rate would fall below 34%.

Statistical analysis

For the primary endpoint analysis, the observed SAE rate will be reported with a 95% CI. The decision criterion is whether the upper bound of this CI is below 34%.

Secondary and exploratory outcomes, including biomarkers, HRV, morphological stellate ganglion changes on MRI and KCCQ-23 scores, will be summarised descriptively using appropriate summary statistics. Where appropriate, exploratory paired statistical tests may be used to assess within-patient changes from baseline.

Safety monitoring

As this is an event-driven study, all adverse events will be reviewed by an independent safety monitoring committee consisting of a consultant cardiologist specialising in cardiac devices and electrophysiology and a consultant clinical oncologist specialising in the radiotherapy treatment of head and neck cancers. As per the dose escalation protocol (figure 1), the committee will routinely meet after the completion of each dose of the dose escalation protocol and dose escalation will only occur once the committee is satisfied with safety. In addition, if any SAE is detected during study follow-up visits, this will trigger a

safety committee review and no further participants will receive radiotherapy pending outcome of this review.

Ethics and dissemination

The study design and research protocol were approved by the South Central—Oxford B Research Ethics Committee (REC 24/SC/005) and informed consent (Data online supplemental file 4) will be obtained from all participants. This study is being conducted in accordance with UK laws, Good Clinical Practice and the Declaration of Helsinki 2002. Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise and explain the research to clinicians, commissioners and service users.

DISCUSSION

Consistently, measures of autonomic function have revealed a state of sympathetic activation and vagal withdrawal in cardiac disease,^{38 39 114} which is predictive of mortality and SCD in patients with cardiac disease.^{115–119} Unsurprisingly, autonomic neuromodulation has become an attractive target in the search for novel therapeutic strategies in cardiac disease, particularly in heart failure.^{120 121}

Attempts to harness the cardioprotective and anti-arrhythmic effects of parasympathetic tone through vagal nerve stimulation have proven challenging. The net cardiac effect of stimulating the vagus nerve, which contains both afferent and efferent nerve fibres, reflects a complex interaction between afferent mediated central inhibition of parasympathetic tone and the direct cardiac effects of efferent fibre stimulation.¹²² Randomised clinical trials of vagal nerve stimulation, each using different stimulation protocols, have resulted in discrepant results and failed to demonstrate substantial clinical benefits in humans.^{123–126}

In contrast, targeting the sympathetic nervous system has proven to be a reliable approach, particularly in preventing VAs. Reducing sympathetic tone through deep sedation or stellate ganglion block is a common guideline endorsed strategy for the management of arrhythmic storm and is associated with consistent reduction in arrhythmia burden.^{72 127} Similarly, a permanent reduction of sympathetic tone through surgical CSD is guideline endorsed for the prevention of SCD in patients with LQTS and CPVT with a similar level of recommendation as ICD implantation.¹²⁷ Increasingly, surgical CSD is also being used to prevent VAs in patients structural heart disease of all aetiologies.^{74 87 128}

The stellate ganglia are an appealing therapeutic target, as the majority of cardiac sympathetic innervation originates here, and they undergo extensive remodelling in cardiac disease that favours sympathetic activation. In stellate ganglia removed from patients with recurrent VAs, sympathetic neurons are larger in size, have increased synaptic density, demonstrate signs of

**Table 2** Study outcome measures

	Outcome	Measure
Primary outcome		
Safety	Treatment-related SAEs	SAEs are defined as any grade 3 toxicity requiring hospitalisation or any grade 4–5 toxicity in the first 6 months as defined by the Common Terminology Criteria for Adverse Events. The relatedness of any SAE will be determined by an independent safety committee.
	Treatment-related side effects not meeting SAE criteria	Patient reported symptoms on symptom questionnaire (data online supplemental file 3). Clinical findings on full cardiovascular and neurological examination.
Secondary outcomes		
Feasibility	Ability to target the stellate ganglia at the protocol prespecified dose	Acceptable visualisation of stellate ganglia on 1.5T baseline MRI. Ability to deliver protocol-specified radiotherapy dose without exceeding the maximum tolerated doses for the ICD device or adjacent organs at risk
Efficacy	Physical modification of the stellate ganglia following treatment	Qualitative and quantitative changes in stellate ganglion morphology at 6-month follow-up 1.5T MRI compared with baseline
	Changes in HRV following treatment	The following HRV metrics will be calculated from R–R intervals from a 10 min, supine, spontaneously breathing recording at every study visit: Frequency domain: power in the LF (0.04–0.15 Hz) and HF (0.15–0.4 Hz) spectral bands, and LF/HF ratio. Time domain: standard deviation of normal–normal intervals (SDNN), root mean square of successive differences (RMSSD), percentage of successive normal–normal intervals that differ by more than 50 ms (pNN50).
	Changes in biomarkers of sympathetic activity following treatment	Circulating plasma epinephrine, norepinephrine and neuropeptide-Y at 6 weeks, 3 months and 6 months compared with baseline.
	Changes in arrhythmia burden following treatment	Number of ventricular arrhythmias requiring ICD therapy in the 6 months preceding radiotherapy compared with 6 months post radiotherapy.
	Changes in patient-reported quality of life following treatment	KCCQ-23 at 6 months post radiotherapy compared with baseline.
HF, high frequency; HRV, heart rate variability; ICD, implantable cardioverter defibrillator; KCCQ-23, Kansas City Cardiomyopathy Questionnaire; LF, low frequency; SAEs, serious adverse events.		

oxidative stress and have adrenergic profiles in keeping with sympathetic activation. This is accompanied by proinflammatory changes such as neutrophil and T-cell infiltration, as well as activation of satellite glia.^{129 130} In animal models of cardiovascular disease, sympathetic neurons in the stellate ganglia show altered ion channel expression predisposing to increased excitability. Single cell messenger RNA sequencing in spontaneously hypertensive rats reveals reduced expression of subunit genes associated with the M current,¹³¹ an inhibitory potassium current which has important influence on neuron resting potential and restricting neuron firing.¹³² Similarly, in rats with ischaemic cardiomyopathy, there is enhanced sympathetic excitability due to increased N-Type calcium currents.¹³³

Additionally, the role of satellite glial cells in the stellate ganglia in mediating sympathoexcitation is being increasingly recognised. Each sympathetic neuron is associated with its own satellite glial which envelops the cell body and its synaptic connections, forming a distinct functional unit. This close association with both cell bodies and synapses suggests that glial cells can modulate neuronal activity

and synaptic transmission.^{134 135} Sympathetic glia are sensitive to acetylcholine (the primary neurotransmitter at the pre–post ganglionic synapse)¹³⁶ and release factors that augment cholinergic transmission, promote synapse formation, contribute to neuronal survival and modulate neuronal metabolism and neurotransmitter homeostats.^{137 138} The importance of satellite glia is reinforced by single cell transcriptomic analysis which reveals diverse phenotypes of glia, with transcriptomic profiles suggesting functions such as neuronal repair, regulation of neuronal metabolism, immune response and regulation of extracellular ion concentrations.¹³⁹ In mice, while glia normally act to restrain sympathetic activity,¹³⁷ glial activation in the stellate ganglia enhances sympathetic output to the heart, increasing heart rate and myocardial contraction and cardiac norepinephrine release.¹⁴⁰ Furthermore, sympathetic nerve damage activates glia in sympathetic ganglia, providing a mechanism through which cardiac damage may trigger glial activation and stellate ganglion remodelling.¹⁴¹

Radiotherapy may be particularly well suited for neuromodulation of the stellate ganglia as glial cells seem to be more radiosensitive than neurons.¹⁴²

Preclinical work has demonstrated that radiotherapy can inhibit satellite glial activation in dorsal root ganglia without impairing sensory or motor neuronal function.¹⁰² In parallel, the anti-inflammatory effects of low dose radiotherapy are well established and have been exploited therapeutically in a range of inflammatory conditions.¹⁴³ Notably, a surprising finding from cardiac radiotherapy trials is that low dose whole heart radiotherapy improves cardiac function through anti-inflammatory effects.¹⁴⁴ Furthermore, doses of approximately 25 Gy used in most cardiac radiotherapy studies to date are below the threshold associated with cardiac fibrosis. Instead, antiarrhythmic effects at these doses likely arise from alterations in cardiomyocyte gene expression, including of ion channels and gap junction proteins, thus changing their electrophysiological properties.^{145 146} Current evidence thus supports the hypothesis that subablative radiation doses may be sufficient to modulate sympathetic output through combined anti-inflammatory, glial-suppressive and transcriptional mechanisms, without causing irreversible neuronal injury. As such, radiotherapy may offer a safer alternative to surgical CSD, with the potential to minimise procedure-related morbidity while preserving therapeutic efficacy.

However, as the use of radiotherapy to the stellate ganglia for the treatment of VA is novel, both the nature and incidence of complications are unknown. Overall rates of complications reported in surgical CSD series are very variable, though off-site neurological effects are consistently the most common.^{87 88 147} Altered sensation, temperature regulation or reduced sweating in the arm or face are reported in up to 70% of patients, while acute Horner's syndrome occurs in up to 20% of patients but persists in less than 10%.⁸⁸ Many of these complications are at least in part due to physical manipulation or inadvertent injury to adjacent neural structures during surgery.^{80 148 149} We therefore anticipate fewer off-site neurological effects by virtue of our non-invasive approach. Furthermore, surgical complications, including pneumothorax, haemothorax and wound infections, which occur in up to 15% of patients,⁸⁷ would be avoided entirely. Indeed, in the only published case series of radiotherapy to the stellate ganglia, three patients underwent 40 Gy stereotactic radiosurgery bilaterally to the stellate ganglia for refractory angina with no acute or periprocedural complications reported.¹⁵⁰

Expected self-limiting adverse effects of cervical radiotherapy include fatigue, skin irritation and mucositis leading to cough, difficulty in swallowing or indigestion.^{109 151} Severe complications such as oesophageal fistulas or strictures are unlikely at doses below 60 Gy and the expected frequency in our study is well below 5%.¹⁵² Finally, stochastic effects of ionising radiation such as secondary malignancy may manifest after many years or decades. However,

given the poor prognosis of patients with severe heart failure and recurrent VAs—with mortality rates of over 50% at 5 years¹⁵³—such late effects may never become clinically apparent.

In this context, the RADIO-STAR study will provide critical first-in-human safety data and radiotherapy dose information for stellate ganglion targeting. These findings will be essential for informing the design of future larger-scale randomised trials aimed at evaluating the efficacy and durability of this novel neuromodulatory approach.

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REFERENCES

- 1 Adabag AS, Luepker RV, Roger VL, *et al*. Sudden cardiac death: epidemiology and risk factors. *Nat Rev Cardiol* 2010;7:216–25.



- 2 Paratz ED, Rowsell L, Zentner D, *et al.* Cardiac arrest and sudden cardiac death registries: a systematic review of global coverage. *Open Heart* 2020;7:e001195.
- 3 Bozkurt B, Ahmad T, Alexander KM, *et al.* Heart Failure Epidemiology and Outcomes Statistics: A Report of the Heart Failure Society of America. *J Card Fail* 2023;29:1412–51.
- 4 Shen L, Jhund PS, Petrie MC, *et al.* Declining Risk of Sudden Death in Heart Failure. *N Engl J Med* 2017;377:41–51.
- 5 Bardy GH, Lee KL, Mark DB, *et al.* Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225–37.
- 6 Moss AJ, Zareba W, Hall WJ, *et al.* Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877–83.
- 7 Poole JE, Johnson GW, Hellkamp AS, *et al.* Prognostic importance of defibrillator shocks in patients with heart failure. *N Engl J Med* 2008;359:1009–17.
- 8 Sears SF, Rosman L, Sasaki S, *et al.* Defibrillator shocks and their effect on objective and subjective patient outcomes: Results of the PainFree SST clinical trial. *Heart Rhythm* 2018;15:734–40.
- 9 Perini AP, Kutryfa V, Veazie P, *et al.* Effects of implantable cardioverter/defibrillator shock and antitachycardia pacing on anxiety and quality of life: A MADIT-RIT substudy. *Am Heart J* 2017;189:75–84.
- 10 Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *The Lancet* 1999;353:2001–7.
- 11 The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *The Lancet* 1999;353:9–13.
- 12 Mason JW. A comparison of seven antiarrhythmic drugs in patients with ventricular tachyarrhythmias. Electrophysiologic Study versus Electrocardiographic Monitoring Investigators. *N Engl J Med* 1993;329:452–8.
- 13 Singh SN, Fletcher RD, Fisher SG, *et al.* Amiodarone in Patients with Congestive Heart Failure and Asymptomatic Ventricular Arrhythmia. *N Engl J Med* 1995;333:77–82.
- 14 Connolly SJ, Dorian P, Roberts RS, *et al.* Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. *JAMA* 2006;295:165–71.
- 15 Markman TM. Catheter Ablation for Ventricular Tachycardia - The Case for Earlier Intervention. *N Engl J Med* 2025;392:818–9.
- 16 Echt DS, Liebson PR, Mitchell LB, *et al.* Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991;324:781–8.
- 17 Stanton MS, Prystowsky EN, Fineberg NS, *et al.* Arrhythmogenic effects of antiarrhythmic drugs: A study of 506 patients treated for ventricular tachycardia or fibrillation. *J Am Coll Cardiol* 1989;14:209–15.
- 18 Konstantopoulou A, Tsirikas S, Asvestas D, *et al.* Mechanisms of drug-induced proarrhythmia in clinical practice. *WJC* 2013;5:175.
- 19 Shivkumar K. Catheter Ablation of Ventricular Arrhythmias. *N Engl J Med* 2019;380:1555–64.
- 20 Kuck K-H, Schaumann A, Eckardt L, *et al.* Catheter ablation of stable ventricular tachycardia before defibrillator implantation in patients with coronary heart disease (VTACH): a multicentre randomised controlled trial. *The Lancet* 2010;375:31–40.
- 21 Kuck K-H, Titz RR, Deneke T, *et al.* Impact of Substrate Modification by Catheter Ablation on Implantable Cardioverter-Defibrillator Interventions in Patients With Unstable Ventricular Arrhythmias and Coronary Artery Disease: Results From the Multicenter Randomized Controlled SMS (Substrate Modification Study). *Circ Arrhythm Electrophysiol* 2017;10:e004422.
- 22 Reddy VY, Reynolds MR, Neuzil P, *et al.* Prophylactic catheter ablation for the prevention of defibrillator therapy. *N Engl J Med* 2007;357:2657–65.
- 23 Sapp JL, Wells GA, Parkash R, *et al.* Ventricular Tachycardia Ablation versus Escalation of Antiarrhythmic Drugs. *N Engl J Med* 2016;375:111–21.
- 24 Sapp JL, Tang ASL, Parkash R, *et al.* Catheter Ablation or Antiarrhythmic Drugs for Ventricular Tachycardia. *N Engl J Med* 2025;392:737–47.
- 25 Curtain JP, Docherty KF, Jhund PS, *et al.* Effect of dapagliflozin on ventricular arrhythmias, resuscitated cardiac arrest, or sudden death in DAPA-HF. *Eur Heart J* 2021;42:3727–38.
- 26 Moss AJ, Schuger C, Beck CA, *et al.* Reduction in Inappropriate Therapy and Mortality through ICD Programming. *N Engl J Med* 2012;367:2275–83.
- 27 Banner NR, Bonser RS, Clark AL, *et al.* UK guidelines for referral and assessment of adults for heart transplantation. *Heart* 2011;97:1520–7.
- 28 Rajendran PS, Challis RC, Fowlkes CC, *et al.* Identification of peripheral neural circuits that regulate heart rate using optogenetic and viral vector strategies. *Nat Commun* 2019;10:1944.
- 29 Hanna P, Dacey MJ, Brennan J, *et al.* Innervation and Neuronal Control of the Mammalian Sinoatrial Node a Comprehensive Atlas. *Circ Res* 2021;128:1279–96.
- 30 Levy MN. Sympathetic-parasympathetic interactions in the heart. *Circ Res* 1971;29:437–45.
- 31 Levy MN, Ng M, Martin P, *et al.* Sympathetic and Parasympathetic Interactions upon the Left Ventricle of the Dog. *Circ Res* 1966;19:5–10.
- 32 Shiferaw Y, Aistrup GL, Wasserstrom JA. Intracellular Ca²⁺ waves, afterdepolarizations, and triggered arrhythmias. *Cardiovasc Res* 2012;95:265–8.
- 33 Yagishita D, Chui RW, Yamakawa K, *et al.* Sympathetic nerve stimulation, not circulating norepinephrine, modulates T-peak to T-end interval by increasing global dispersion of repolarization. *Circ Arrhythm Electrophysiol* 2015;8:174–85.
- 34 Priori SG, Mantica M, Schwartz PJ. Delayed afterdepolarizations elicited in vivo by left stellate ganglion stimulation. *Circulation* 1988;78:178–85.
- 35 Kollai M, Koizumi K. Reciprocal and non-reciprocal action of the vagal and sympathetic nerves innervating the heart. *J Auton Nerv Syst* 1979;1:33–52.
- 36 Levy MN, Martin PJ. Autonomic neural control of cardiac function. In: *Physiology and Pathophysiology of the Heart*. Springer, 1989: 361–79.
- 37 Corr PB, Gillis RA. Autonomic neural influences on the dysrhythmias resulting from myocardial infarction. *Circ Res* 1978;43:1–9.
- 38 Florea VG, Cohn JN. The autonomic nervous system and heart failure. *Circ Res* 2014;114:1815–26.
- 39 Malliani A, Schwartz PJ, Zanchetti A. A sympathetic reflex elicited by experimental coronary occlusion. *Am J Physiol* 1969;217:703–9.
- 40 Zucker IH, Schultz HD, Li YF, *et al.* The origin of sympathetic outflow in heart failure: the roles of angiotensin II and nitric oxide. *Prog Biophys Mol Biol* 2004;84:217–32.
- 41 Zucker IH, Patel KP, Schultz HD. Neurohumoral stimulation. *Heart Fail Clin* 2012;8:87–99.
- 42 Habecker BA, Bers DM, Birren SJ, *et al.* Molecular and cellular neurocardiology in heart disease. *J Physiol (Lond)* 2025;603:1689–728.
- 43 Tsien RW, Bean BP, Hess P, *et al.* Mechanisms of calcium channel modulation by beta-adrenergic agents and dihydropyridine calcium agonists. *J Mol Cell Cardiol* 1986;18:691–710.
- 44 Lubbe WF, Podzuweit T, Opie LH. Potential arrhythmogenic role of cyclic adenosine monophosphate (AMP) and cytosolic calcium overload: implications for prophylactic effects of beta-blockers in myocardial infarction and proarrhythmic effects of phosphodiesterase inhibitors. *J Am Coll Cardiol* 1992;19:1622–33.
- 45 Sanguinetti MC, Jurkiewicz NK, Scott A, *et al.* Isoproterenol antagonizes prolongation of refractory period by the class III antiarrhythmic agent E-4031 in guinea pig myocytes. Mechanism of action. *Circ Res* 1991;68:77–84.
- 46 Kalla M, Hao G, Tapoulal N, *et al.* The cardiac sympathetic co-transmitter neuropeptide Y is pro-arrhythmic following ST-elevation myocardial infarction despite beta-blockade. *Eur Heart J* 2020;41:2168–79.
- 47 Hoang JD, Salavation S, Yamaguchi N, *et al.* Cardiac sympathetic activation circumvents high-dose beta blocker therapy in part through release of neuropeptide Y. *JCI Insight* 2020;5:e135519.
- 48 Gibbs T, Tapoulal N, Shanmuganathan M, *et al.* Neuropeptide-Y Levels in ST-Segment-Elevation Myocardial Infarction: Relationship With Coronary Microvascular Function, Heart Failure, and Mortality. *J Am Heart Assoc* 2022;11:e024850.
- 49 McDowell K, Adamson C, Jackson C, *et al.* Neuropeptide Y is elevated in heart failure and is an independent predictor of outcomes. *Eur J Heart Fail* 2024;26:107–16.
- 50 Coote JH, Chauhan RA. The sympathetic innervation of the heart: Important new insights. *Auton Neurosci* 2016;199:17–23.
- 51 Buckley U, Yamakawa K, Takamiya T, *et al.* Targeted stellate decentralization: Implications for sympathetic control of ventricular electrophysiology. *Heart Rhythm* 2016;13:282–8.
- 52 Harris AS, Otero H, Bocage AJ. The induction of arrhythmias by sympathetic activity before and after occlusion of a coronary artery in the canine heart. *J Electrocardiol* 1971;4:34–43.
- 53 Schwartz PJ, Vanoli E. Cardiac arrhythmias elicited by interaction between acute myocardial ischemia and sympathetic hyperactivity: a new experimental model for the study of antiarrhythmic drugs. *J Cardiovasc Pharmacol* 1981;3:1251–9.
- 54 Schwartz PJ, Vanoli E, Zaza A, *et al.* The effect of antiarrhythmic drugs on life-threatening arrhythmias induced by the interaction

- between acute myocardial ischemia and sympathetic hyperactivity. *Am Heart J* 1985;109:937–48.
- 55 Ng GA, Mantravadi R, Walker WH, et al. Sympathetic nerve stimulation produces spatial heterogeneities of action potential restitution. *Heart Rhythm* 2009;6:696–706.
- 56 Vaseghi M, Yamakawa K, Sinha A, et al. Modulation of regional dispersion of repolarization and T-peak to T-end interval by the right and left stellate ganglia. *Am J Physiol Heart Circ Physiol* 2013;305:H1020–30.
- 57 Vaseghi M, Lux RL, Mahajan A, et al. Sympathetic stimulation increases dispersion of repolarization in humans with myocardial infarction. *Am J Physiol Heart Circ Physiol* 2012;302:H1838–46.
- 58 Vaseghi M, Zhou W, Shi J, et al. Sympathetic innervation of the anterior left ventricular wall by the right and left stellate ganglia. *Heart Rhythm* 2012;9:1303–9.
- 59 Cao JM, Fishbein MC, Han JB, et al. Relationship between regional cardiac hyperinnervation and ventricular arrhythmia. *Circulation* 2000;101:1960–9.
- 60 Opthof T, Coronel R, Vermeulen JT, et al. Dispersion of refractoriness in normal and ischaemic canine ventricle: effects of sympathetic stimulation. *Cardiovasc Res* 1993;27:1954–60.
- 61 Tomek J, Hao G, Tomková M, et al. β -Adrenergic Receptor Stimulation and Alternans in the Border Zone of a Healed Infarct: An ex vivo Study and Computational Investigation of Arrhythmogenesis. *Front Physiol* 2019;10:350.
- 62 Del Rio CL, Dawson TA, Clymer BD, et al. Effects of acute vagal nerve stimulation on the early passive electrical changes induced by myocardial ischaemia in dogs: heart rate-mediated attenuation. *Exp Physiol* 2008;93:931–44.
- 63 Diaz HS, Toledo C, Andrade DC, et al. Neuroinflammation in heart failure: new insights for an old disease. *J Physiol* 2020;598:33–59.
- 64 Shinlapawittayatorn K, Chinda K, Palee S, et al. Low-amplitude, left vagus nerve stimulation significantly attenuates ventricular dysfunction and infarct size through prevention of mitochondrial dysfunction during acute ischemia-reperfusion injury. *Heart Rhythm* 2013;10:1700–7.
- 65 Beaumont E, Southerland EM, Hardwick JC, et al. Vagus nerve stimulation mitigates intrinsic cardiac neuronal and adverse myocyte remodeling postmyocardial infarction. *Am J Physiol Heart Circ Physiol* 2015;309:H1198–206.
- 66 Nash MP, Thornton JM, Sears CE, et al. Ventricular activation during sympathetic imbalance and its computational reconstruction. *J Appl Physiol* 2001;90:287–98.
- 67 Vanoli E, De Ferrari GM, Stramba-Badiale M, et al. Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. *Circ Res* 1991;68:1471–81.
- 68 Vaseghi M, Salavatian S, Rajendran PS, et al. Parasympathetic dysfunction and antiarrhythmic effect of vagal nerve stimulation following myocardial infarction. *JCI Insight* 2017;2:e86715.
- 69 Bundgaard JS, Jacobsen PK, Grand J, et al. Deep sedation as temporary bridge to definitive treatment of ventricular arrhythmia storm. *Eur Heart J Acute Cardiovasc Care* 2020;9:657–64.
- 70 Bourke T, Vaseghi M, Michowitz Y, et al. Neuraxial modulation for refractory ventricular arrhythmias: value of thoracic epidural anesthesia and surgical left cardiac sympathetic denervation. *Circulation* 2010;121:2255–62.
- 71 Do DH, Bradfield J, Ajijola OA, et al. Thoracic Epidural Anesthesia Can Be Effective for the Short-Term Management of Ventricular Tachycardia Storm. *J Am Heart Assoc* 2017;6:e007080.
- 72 Meng L, Tseng CH, Shivkumar K, et al. Efficacy of Stellate Ganglion Blockade in Managing Electrical Storm: A Systematic Review. *JACC Clin Electrophysiol* 2017;3:942–9.
- 73 Savastano S, Baldi E, Compagnoni S, et al. Electrical storm treatment by percutaneous stellate ganglion block: the STAR study. *Eur Heart J* 2024;45:823–33.
- 74 Vaseghi M, Barwad P, Malavassi Corrales FJ, et al. Cardiac Sympathetic Denervation for Refractory Ventricular Arrhythmias. *J Am Coll Cardiol* 2017;69:3070–80.
- 75 Dacey M, Salahudeen O, Swid MA, et al. Structural and function organization of intrathoracic extracardiac autonomic projections to the porcine heart: Implications for targeted neuromodulation therapy. *Heart Rhythm* 2022;19:975–83.
- 76 Schwartz PJ. Cutting nerves and saving lives. *Heart Rhythm* 2009;6:760–3.
- 77 Wilde AAM, Bhuiyan ZA, Crotti L, et al. Left Cardiac Sympathetic Denervation for Catecholaminergic Polymorphic Ventricular Tachycardia. *N Engl J Med* 2008;358:2024–9.
- 78 Schwartz PJ. Cardiac sympathetic denervation to prevent life-threatening arrhythmias. *Nat Rev Cardiol* 2014;11:346–53.
- 79 Moss AJ, McDonald J. Unilateral Cervicothoracic Sympathetic Ganglionectomy for the Treatment of Long QT Interval Syndrome. *N Engl J Med* 1971;285:903–4.
- 80 Collura CA, Johnson JN, Moir C, et al. Left cardiac sympathetic denervation for the treatment of long QT syndrome and catecholaminergic polymorphic ventricular tachycardia using video-assisted thoracic surgery. *Heart Rhythm* 2009;6:752–9.
- 81 Coleman MA, Bos JM, Johnson JN, et al. Videoscopic left cardiac sympathetic denervation for patients with recurrent ventricular fibrillation/malignant ventricular arrhythmia syndromes besides congenital long-QT syndrome. *Circ Arrhythm Electrophysiol* 2012;5:782–8.
- 82 Dusi V, De Ferrari GM, Pugliese L, et al. Cardiac Sympathetic Denervation in Channelopathies. *Front Cardiovasc Med* 2019;6:27.
- 83 Dusi V, Pugliese L, De Ferrari GM, et al. Left Cardiac Sympathetic Denervation for Long QT Syndrome. *JACC: Clinical Electrophysiology* 2022;8:281–94.
- 84 Zeppenfeld K, Tfelt-Hansen J, Riva M, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Developed by the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC) Endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2022;43:3997–4126.
- 85 Schwartz PJ, Motolese M, Pollavini G, et al. Prevention of Sudden Cardiac Death After a First Myocardial Infarction by Pharmacologic or Surgical Antiadrenergic Interventions. *Cardiovasc electrophysiol* 1992;3:2–16.
- 86 Assis FR, Sharma A, Shah R, et al. Long-Term Outcomes of Bilateral Cardiac Sympathetic Denervation for Refractory Ventricular Tachycardia. *JACC: Clinical Electrophysiology* 2021;7:463–70.
- 87 Shah R, Assis F, Alugubelli N, et al. Cardiac sympathetic denervation for refractory ventricular arrhythmias in patients with structural heart disease: A systematic review. *Heart Rhythm* 2019;16:1499–505.
- 88 Waddell-Smith KE, Ertresvaag KN, Li J, et al. Physical and Psychological Consequences of Left Cardiac Sympathetic Denervation in Long-QT Syndrome and Catecholaminergic Polymorphic Ventricular Tachycardia. *Circ Arrhythm Electrophysiol* 2015;8:1151–8.
- 89 Damiani D, Agosta VT, D'Andrea Urssoleo J, et al. Perioperative and long-term outcomes of bilateral cardiac sympathetic denervation via video-assisted thoracoscopic surgery in patients with refractory ventricular arrhythmias. *Int J Cardiol* 2025;421:132890.
- 90 Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: The report of AAPM Task Group 101. *Med Phys* 2010;37:4078–101.
- 91 Franzese C, Balermipas P. Stereotactic ablative radiotherapy for treating primary head and neck cancer and locoregional recurrence: A comprehensive review of the literature. *Clin Transl Radiat Oncol* 2024;46:100766.
- 92 Timmerman R, Kavanagh B. Stereotactic Body Radiation Therapy. *Curr Probl Cancer* 2005;29:120–57.
- 93 Chan A-W, Boutron I, Hopewell S, et al. SPIRIT 2025 statement: updated guideline for protocols of randomised trials. *BMJ* 2025;389:e081477.
- 94 Diez P, Hanna GG, Aitken KL, et al. UK 2022 Consensus on Normal Tissue Dose-Volume Constraints for Oligometastatic, Primary Lung and Hepatocellular Carcinoma Stereotactic Ablative Radiotherapy. *Clin Oncol* 2022;34:288–300.
- 95 Maier JG, Perry RH, Saylor W, et al. Radiation Myelitis of the Dorsolumbar Spinal Cord. *Radiology* 1969;93:153–60.
- 96 Parsons JT, Bova FJ, Fitzgerald CR, et al. Radiation optic neuropathy after megavoltage external-beam irradiation: analysis of time-dose factors. *Int J Radiat Oncol Biol Phys* 1994;30:755–63.
- 97 Stoll BA, Andrews JT. Radiation-induced Peripheral Neuropathy. *Br Med J* 1966;1:834–7.
- 98 Salazar OM, Rubin P, Feldstein ML, et al. High dose radiation therapy in the treatment of malignant gliomas: final report. *Int J Radiat Oncol Biol Phys* 1979;5:1733–40.
- 99 Hudec M, Jiravsky O, Spacek R, et al. Chronic refractory angina pectoris treated by bilateral stereotactic radiosurgical stellate ganglion ablation: first-in-man case report. *Eur Heart J Case Rep* 2021;5:ytab184.
- 100 Tuleasca C, Paddick I, Hopewell JW, et al. Establishment of a Therapeutic Ratio for Gamma Knife Radiosurgery of Trigeminal Neuralgia: The Critical Importance of Biologically Effective Dose Versus Physical Dose. *World Neurosurg* 2020;134:e204–13.



- 101 Tuleasca C, Régis J, Sahgal A, *et al.* Stereotactic radiosurgery for trigeminal neuralgia: a systematic review. *J Neurosurg* 2019;130:733–57.
- 102 Goldschmidt E, Fellows-Mayle W, Wolfe R, *et al.* Radiosurgery to the spinal dorsal root ganglion induces fibrosis and inhibits satellite glial cell activation while preserving axonal neurotransmission. *J Neurosurg Spine* 2020;32:790–8.
- 103 Storer BE. Design and Analysis of Phase I Clinical Trials. *Biometrics* 1989;45:925.
- 104 Le Tourneau C, Lee JJ, Siu LL. Dose Escalation Methods in Phase I Cancer Clinical Trials. *J Natl Cancer Inst* 2009;101:708–20.
- 105 Miften M, Mihailidis D, Kry SF, *et al.* Management of radiotherapy patients with implanted cardiac pacemakers and defibrillators: A Report of the AAPM TG-203[†]. *Med Phys Mex Symp Med Phys* 2019;46:e757–88.
- 106 Working Group comprised of the Royal College of Radiologists Radiotherapy Board BC-OSaBHRS. Guidance on the management of patients with cardiac implantable electronic devices receiving radiotherapy. 2025.
- 107 Gogineni E, Rana Z, Vempati P, *et al.* Stereotactic body radiotherapy as primary treatment for elderly and medically inoperable patients with head and neck cancer. *Head & Neck* 2020;42:2880–6.
- 108 Antiel RM, Bos JM, Joyce DD, *et al.* Quality of life after videoscopic left cardiac sympathetic denervation in patients with potentially life-threatening cardiac channelopathies/cardiomyopathies. *Heart Rhythm* 2016;13:62–9.
- 109 Singer S, Amdal CD, Hammerlid E, *et al.* International validation of the revised European Organisation for Research and Treatment of Cancer Head and Neck Cancer Module, the EORTC QLQ-HN43: Phase IV. *Head & Neck* 2019;41:1725–37.
- 110 Joseph SM, Novak E, Arnold SV, *et al.* Comparable Performance of the Kansas City Cardiomyopathy Questionnaire in Patients With Heart Failure With Preserved and Reduced Ejection Fraction. *Circ: Heart Failure* 2013;6:1139–46.
- 111 Nassif M, Fine JT, Dolan C, *et al.* Validation of the Kansas City Cardiomyopathy Questionnaire in Symptomatic Obstructive Hypertrophic Cardiomyopathy. *JACC: Heart Failure* 2022;10:531–9.
- 112 Green CP, Porter CB, Bresnahan DR, *et al.* Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol* 2000;35:1245–55.
- 113 Spertus JA, Jones PG, Sandhu AT, *et al.* Interpreting the Kansas City Cardiomyopathy Questionnaire in Clinical Trials and Clinical Care. *J Am Coll Cardiol* 2020;76:2379–90.
- 114 Bussmann B, Ayagama T, Liu K, *et al.* Bayliss Starling Prize Lecture 2023: Neuropeptide-Y being ‘unsympathetic’ to the broken hearted. *J Physiol (Lond)* 2025;603:1841–64.
- 115 Cole CR, Blackstone EH, Pashkow FJ, *et al.* Heart-Rate Recovery Immediately after Exercise as a Predictor of Mortality. *N Engl J Med* 1999;341:1351–7.
- 116 De Ferrari GM, Sanzo A, Bertoletti A, *et al.* Baroreflex Sensitivity Predicts Long-Term Cardiovascular Mortality After Myocardial Infarction Even in Patients With Preserved Left Ventricular Function. *J Am Coll Cardiol* 2007;50:2285–90.
- 117 La Rovere MT, Bigger JT Jr, Marcus FI, *et al.* Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet* 1998;351:478–84.
- 118 Fallavollita JA, Dare JD, Carter RL, *et al.* Denervated Myocardium Is Preferentially Associated With Sudden Cardiac Arrest in Ischemic Cardiomyopathy: A Pilot Competing Risks Analysis of Cause-Specific Mortality. *Circ Cardiovasc Imaging* 2017;10:e006446.
- 119 La Rovere MT, Pinna GD, Maestri R, *et al.* Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation* 2003;107:565–70.
- 120 Ajjola OA, Aksu T, Arora R, *et al.* Clinical neurocardiology: defining the value of neuroscience-based cardiovascular therapeutics – 2024 update. *J Physiol (Lond)* 2025;603:1781–839.
- 121 Herring N, Ajjola OA, Foreman RD, *et al.* Neurocardiology: translational advancements and potential. *J Physiol (Lond)* 2025;603:1729–79.
- 122 Ardell JL, Nier H, Hammer M, *et al.* Defining the neural fulcrum for chronic vagus nerve stimulation: implications for integrated cardiac control. *J Physiol (Lond)* 2017;595:6887–903.
- 123 Zannad F, De Ferrari GM, Tuinenburg AE, *et al.* Chronic vagal stimulation for the treatment of low ejection fraction heart failure: results of the NEURAL Cardiac TherApy foR Heart Failure (NECTAR-HF) randomized controlled trial. *Eur Heart J* 2015;36:425–33.
- 124 Gold MR, Van Veldhuisen DJ, Hauptman PJ, *et al.* Vagus Nerve Stimulation for the Treatment of Heart Failure: The INOVATE-HF Trial. *J Am Coll Cardiol* 2016;68:149–58.
- 125 Premchand RK, Sharma K, Mittal S, *et al.* Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: results of the ANTHEM-HF trial. *J Card Fail* 2014;20:808–16.
- 126 Konstam M, Udelson J, Mann D, *et al.* Autonomic Regulation Therapy To Improve Symptoms And Clinical Outcomes In Patients With Heart Failure And Reduced Ejection Fraction (ANTHEM-HFrEF) Pivotal Study Results. *J Card Fail* 2024;30:313.
- 127 Zeppenfeld K, Tfelt-Hansen J, de Riva M, *et al.* 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2022;43:3997–4126.
- 128 Ahmed A, Charate R, Bawa D, *et al.* Bilateral Cardiac Sympathetic Denervation for Refractory Multifocal Premature Ventricular Contractions in Patients With Nonischemic Cardiomyopathy. *JACC: Clinical Electrophysiology* 2024;10:31–9.
- 129 Ajjola OA, Hoover DB, Simerly TM, *et al.* Inflammation, oxidative stress, and glial cell activation characterize stellate ganglia from humans with electrical storm. *JCI Insight* 2017;2:e94715.
- 130 Rizzo S, Basso C, Troost D, *et al.* T-cell-mediated inflammatory activity in the stellate ganglia of patients with ion-channel disease and severe ventricular arrhythmias. *Circ Arrhythm Electrophysiol* 2014;7:224–9.
- 131 Davis H, Herring N, Paterson DJ. Downregulation of M Current Is Coupled to Membrane Excitability in Sympathetic Neurons Before the Onset of Hypertension. *Hypertension* 2020;76:1915–23.
- 132 Wladyka CL, Kunze DL. KCNQ/M-currents contribute to the resting membrane potential in rat visceral sensory neurons. *J Physiol* 2006;575:175–89.
- 133 Tu H, Liu J, Zhang D, *et al.* Heart failure-induced changes of voltage-gated Ca²⁺ channels and cell excitability in rat cardiac postganglionic neurons. *Am J Physiol Cell Physiol* 2014;306:C132–42.
- 134 Hanani M, Spray DC. Emerging importance of satellite glia in nervous system function and dysfunction. *Nat Rev Neurosci* 2020;21:485–98.
- 135 Hanani M. Satellite glial cells in sympathetic and parasympathetic ganglia: in search of function. *Brain Res Rev* 2010;64:304–27.
- 136 Feldman-Goriachnik R, Wu B, Hanani M. Cholinergic responses of satellite glial cells in the superior cervical ganglia. *Neurosci Lett* 2018;671:19–24.
- 137 Mapps AA, Boehm E, Beier C, *et al.* Satellite glia modulate sympathetic neuron survival, activity, and autonomic function. *Elife* 2022;11:e74295.
- 138 Enes J, Haburčák M, Sona S, *et al.* Satellite glial cells modulate cholinergic transmission between sympathetic neurons. *PLoS One* 2020;15:e0218643.
- 139 Mapps AA, Thomsen MB, Boehm E, *et al.* Diversity of satellite glia in sympathetic and sensory ganglia. *Cell Rep* 2022;38:110328.
- 140 Xie AX, Lee JJ, McCarthy KD. Ganglionic GFAP+ glial Gq-GPCR signaling enhances heart functions in vivo. *JCI Insight* 2017;2:e90565.
- 141 Feldman-Goriachnik R, Hanani M. The effects of sympathetic nerve damage on satellite glial cells in the mouse superior cervical ganglion. *Auton Neurosci* 2019;221:102584.
- 142 Kudo S, Suzuki Y, Noda SE, *et al.* Comparison of the radiosensitivities of neurons and glial cells derived from the same rat brain. *Exp Ther Med* 2014;8:754–8.
- 143 Calabrese E, Dhawan G, Kapoor R, *et al.* Radiotherapy treatment of human inflammatory diseases and conditions: Optimal dose. *Hum Exp Toxicol* 2019;38:888–98.
- 144 Pedersen LN, Valenzuela Ripoll C, Ozcan M, *et al.* Cardiac radiation improves ventricular function in mice and humans with cardiomyopathy. *Med* 2023;4:928–43.
- 145 Zhang DM, Navara R, Yin T, *et al.* Cardiac radiotherapy induces electrical conduction reprogramming in the absence of transmural fibrosis. *Nat Commun* 2021;12:5558.
- 146 Mages C, Gamp H, Rahm A-K, *et al.* Cardiac stereotactic body radiotherapy to treat malignant ventricular arrhythmias directly affects the cardiomyocyte electrophysiology. *Heart Rhythm* 2025;22:90–9.
- 147 Gossot D, Kabiri H, Caliandro R, *et al.* Early complications of thoracic endoscopic sympathectomy: a prospective study of 940 procedures. *Ann Thorac Surg* 2001;71:1116–9.
- 148 Odero A, Bozzani A, De Ferrari GM, *et al.* Left cardiac sympathetic denervation for the prevention of life-threatening arrhythmias: The surgical supraclavicular approach to cervicothoracic sympathectomy. *Heart Rhythm* 2010;7:1161–5.
- 149 Miyazaki T, Sakai T, Tsuchiya T, *et al.* Assessment and follow-up of intercostal nerve damage after video-assisted thoracic surgery. *Eur J Cardiothorac Surg* 2011;39:1033–9.

- 150 Cvek J, Jiravsky O, Knybel L, *et al*. Stereotactic radiosurgery as neuromodulation of refractory angina: an initial case series. *Radiat Oncol* 2025;20:33.
- 151 Gharzai LA, Mierzwa ML, Peipert JD, *et al*. Monitoring Adverse Effects of Radiation Therapy in Patients With Head and Neck Cancer: The FACT-HN-RAD Patient-Reported Outcome Measure. *JAMA Otolaryngol Head Neck Surg* 2023;149:884–90.
- 152 Spaulding SL, Ansari E, Xing MH, *et al*. Diagnosis and management of pharyngoesophageal stenosis: A comprehensive approach to prophylactic, endoscopic, and reconstructive treatment options. *Am J Otolaryngol* 2021;42:103003.
- 153 Saxon LA, Hayes DL, Gilliam FR, *et al*. Long-Term Outcome After ICD and CRT Implantation and Influence of Remote Device Follow-Up. *Circulation* 2010;122:2359–67.