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Noninvasive Cardiac Radioablation for Ventricular Arrhythmias

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Abstract

Purpose of Review In this review, we describe the general principles and clinical use of stereotactic radioablation (SR) and its specific application to the treatment of malignant cardiac ventricular arrhythmias, or stereotactic arrhythmia radioablation (STAR). The principles of STAR, and the unmet needs in cardiac arrhythmia ablation are described. The basic pathophysiology of radioablative effect on cardiac tissues, the clinical experience to date, and future directions are discussed.

Recent Findings Basic preclinical research has demonstrated in large animal models (porcine, canine) that delivery of SR energy to cardiac targets, specifically left atrial ablation for atrial fibrillation, results in physiologic and histopathologic evidence of treatment effect without evidence of harm. Clinical treatments delivering SR to ventricular and atrial targets for ventricular tachycardia (VT) and atrial fibrillation (AF) have demonstrated clinical response without evidence of obvious harm or complication thus far.

Summary In the nascent but exciting field of stereotactic radioablation for treatment of cardiac arrhythmias, preclinical evidence has demonstrated treatment effect without to date risk of significant collateral injury. In limited clinical experience treating both ventricular and atrial arrhythmias, clinical benefit in arrhythmia reduction without notable risk of complication has been observed. Further basic mechanistic research, refinement of delivery approaches, and further clinical experience are all anticipated and needed.

Keywords Stereotactic radioablation · Cardiac arrhythmias · Noninvasive ablation · Ventricular tachycardia

Abbreviations

3D-CRT	3-Dimensional conformal radiation therapy
AF	Atrial fibrillation
CT	Computerized tomography
CTV	Clinical target volume
DCM	Dilated cardiomyopathy
EAM	Electroanatomic mapping
ECGI	Electrocardiographic imaging
EPS	Electrophysiology study
ICD	Implantable cardiac defibrillator
ICM	Ischemic cardiomyopathy
IGRT	Image-guided radiation therapy
IMRT	Intensity-modulated radiotherapy
ITV	Internal target volume
MR	Magnetic resonance
NICM	Non-ischemic dilated cardiomyopathy
PET	Positron emission tomography
SBRT	Stereotactic body radiotherapy
SHD	Structural heart disease
SR	Stereotactic radioablation
STAR	Stereotactic arrhythmia radioablation
TCEA	Transcoronary ethanol ablation
PPM	Permanent pacemaker
PTV	Planning target volume
PVC	Premature ventricular complexes
RF	Radiofrequency
RT	Radiation therapy
VA	Ventricular arrhythmia
VF	Ventricular fibrillation
VT	Ventricular tachycardia

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Introduction

Catheter ablation represents a key therapeutic option in the management of ventricular arrhythmias. The majority of ablations are performed using a catheter employing unipolar radiofrequency (RF) energy to heat tissue, leading to necrosis and disruption of the arrhythmogenic tissue [1, 2]. However, catheter ablation is invasive, with risks including vascular injury, thromboembolism, and cardiac tamponade. Arrhythmogenic circuits are often inaccessible with conventional ablation tools and techniques, as they may be deep within the intramural myocardium. In patients with structural heart disease (SHD) where VT was induced and mappable, Tokuda et al. [3] identified this as the most common reason for failed endocardial ablation, with Kumar et al. reporting similar results [4].

To access and target these non-endocardial arrhythmogenic substrates, several strategies have emerged. Epicardial circuits may be accessed via an epicardial approach. However, epicardial access cannot be achieved in approximately 10% [5], most commonly in patients with previous cardiac surgery or pericarditis which has led to epicardial adhesions. In these cases, surgical access may be utilized, but this is more invasive [5, 6]. Epicardial ablation also does not enable ablation of midmyocardial targets.

Transcoronary ethanol ablation (TCEA) [2, 7], coronary coil embolization [2], bipolar radiofrequency ablation [2], and needle catheter ablation [8] techniques have been described as options for ablation of deep circuits. However, each has their limitations as we have previously discussed [1]. Given the limitations of these approaches, a noninvasive means of targeting arrhythmogenic cardiac tissue at any depth within the myocardium has potential significant advantage. It is this desire that has led to the development of a new noninvasive approach utilizing ionizing radiation therapy delivered utilizing a specialized technique to cardiac tissue termed cardiac stereotactic arrhythmia radioablation (STAR).

A Brief Overview of STAR

Radiation therapy (RT) has been mainly utilized to treat malignant or benign tumors, and currently is most commonly delivered via a linear accelerator, a device that generates and shapes beams of high energy, ionizing photon radiation. Modern linear accelerators are mounted either on a gantry or robotic arm to enable treatment delivery from multiple angles around a patient and have built in X-ray-based imaging devices to allow more accurate and precise targeting of the tumor.

Historically (pre-1990s), radiation therapy was delivered with large treatment fields due to lack of image-guidance and lack of 3-dimensional imaging for treatment planning. These historic techniques were relatively imprecise, directing photons at the target tissue but also irradiating a significant amount of healthy surrounding tissue, leading to potential collateral injury and side effects. Small daily doses were used (e.g., 1.8–2 Gray) to allow normal tissue to repair between treatments, and typical curative radiation treatment courses would last 5–7 weeks in an attempt to deliver sufficient dose for tumor control.

The addition of 3-dimensional imaging in the early 1990s for radiation therapy planning (e.g., computed tomography (CT) or magnetic resonance (MR) imaging) substantially improved the radiation therapy targeting process by allowing more direct visualization of tumor targets and surrounding organs, leading to the development of 3-dimensional conformal radiation therapy (3D-CRT), which entailed shaping the radiation beams more conformally around the tumor and excluding adjacent organs. Further advances in the late 1990s included development of intensity modulated radiotherapy (IMRT), which takes the concept of 3D-CRT further and enables modulation of the intensity of radiation within each beam. The technique further improves target dose conformality, while improving sparing of surrounding tissues.

Additional hardware advances in the late 1990s included addition of diagnostic quality X-ray imaging devices directly to the linear accelerators, allowing image-guided radiation therapy (IGRT), which involves performing an orthogonal pair of radiographs or a cone-beam CT directly prior to radiation delivery for target alignment. Robotic controlled tables were developed that allowed high-precision positioning of patients in the treatment room. These advances enable precise alignment of the patient and tumor location immediately before delivery. Additionally, for targets in the thorax and upper abdomen, which may exhibit substantial respiratory motion, motion management techniques including respiratory-gated 4D-CT scans, tumor tracking, and/or respiratory-gated treatments have been developed.

The synthesis of the above techniques led to the development of stereotactic body radiotherapy (SBRT) in the late 1990s and early 2000s, which generally uses IMRT to deliver high dose radiation (e.g. 18Gyx3 fractions, 34Gyx1 fraction) to small targets in the body with high precision and conformality. The application of SBRT to early stage non-small cell lung cancer (Baumann, Nyman et al. 2009, Timmerman, Paulus et al. 2010) has been transformative, and led to high rates of tumor control with low rates of severe toxicity.

Stereotactic arrhythmia radioablation (STAR), refers to the use of SBRT for ablating arrhythmogenic tissue within the heart. Unlike traditional catheter ablation, where mapping and disruption of the arrhythmogenic circuit occur within the procedure, STAR relies on precise definition of an arrhythmogenic target before the delivery of radiation therapy. A three-dimensional treatment plan can then be produced, which

defines the areas of the myocardium which will receive high-dose radiotherapy.

Current Experience

To date, four groups have published outcomes of STAR for VT, from the USA, Switzerland, and Czech Republic. One case series of five patients has been reported in full [9••], with two further case series of three [10••] and five [11] patients published as abstracts (the former of which includes a case previously published as a case report [12], and the latter of which consists of the same five patients subsequently published in full [9••]. Two further cases have been reported [13••, 14]. This leads to a total of ten patients for whom data is available (Table 1). Additional patients are being evaluated and treated through at least two FDA-guided IDE Pilot study NCT02661048 at the time of this writing.

All studies enlisted patients with VT refractory to anti-arrhythmic medication and catheter ablation, or patients ineligible for catheter ablation. Nine patients had SHD, the majority of which was non-ischemic. One patient had idiopathic VT, the arrhythmogenic substrate of which was not amenable to traditional catheter ablation. Jumeau et al. report the only case of STAR being used in the intensive care setting for intractable VT storm [13••].

Substrate identification ideally utilizes a combination of anatomical and electrical mapping. All studies utilized an imaging modality such as contrast MRI or positron emission tomography (PET) to identify scar tissue. However, electrical mapping varied. The Washington U. group [9••, 11] utilized electrocardiographic imaging (ECGI), while other centers used previous electroanatomic mapping (EAM) or relied on anatomic substrate identification.

The radiation techniques utilized thus far can be broadly divided into two treatment approaches, which differ by linear accelerator platform and motion management approach: (1) CyberKnife (Accuray, Sunnyvale, CA)-based treatment delivery with cardiac fiducial marker tracking to compensate for target motion; versus (2) conventional linear accelerator-based treatment delivery with respiratory-gated 4D-CT for target definition to encompass the internal target volume (ITV) of the abnormal cardiac tissue throughout the respiratory cycle.

The CyberKnife device includes a linear accelerator mounted on a robotic arm that can compensate for respiratory motion by tracking the beam to a target region utilizing external surrogate markers and an internal metal fiducial marker during the delivery of radiation therapy. This approach currently requires placement of a metal-tipped intra-cardiac catheter during the radiation planning and treatment delivery process, and treatment delivery times of 45 min to 1.5 h due to the tracking algorithm only permitting the treatment beam to activate within tight marker localization parameters. In comparison, the approach of modeling the respiratory motion and treatment target location throughout the respiratory cycle results in larger target volumes but shorter treatment times. All studies utilized a single radiation dose of 25 Gy, derived from pre-clinical animal model experiments demonstrating ablation of cardiac conduction at this dose [15, 16].

All studies reported reduced arrhythmia burden post STAR. This benefit has been consistently demonstrated to occur earlier than would be predicted if radiation-induced fibrosis was the sole underlying mechanism [9••, 13••, 14].

Longer-term results have also been promising, with the majority of patients having a consistently reduced VT burden. Recurrence was seen in one patient at 9 months in the context of exacerbation on chronic obstructive pulmonary disease [12]. Another underwent catheter ablation at 4 weeks post STAR due to incomplete VT control; VT episodes had decreased, however, from 2000 to 355 in the month pre and post STAR [9••].

The safety profile of STAR has thus far been excellent. One patient was reported to have an ischemic stroke not clearly procedurally related 3 weeks post STAR [9••, 11]. Follow-up imaging has demonstrated pulmonary parenchymal inflammatory changes which appear to resolve by 1 year and is typical of that seen in SBRT for lung cancer [9••]. Echocardiography, where performed, has demonstrated no pericardial effusions and overall improvement in systolic function post STAR [9••, 12]. Minimal rise in troponin was demonstrated by Cvek et al. [14]. No complications have been reported in patients post STAR due to implantable cardioverter defibrillator (ICD) malfunction and the techniques utilized with SBRT typically.

Our Recommended Approach to STAR

The Multidisciplinary Team

An effective and safe STAR program will require multidisciplinary collaboration between electrophysiology, radiation oncology, and imaging services. In the delivery of SBRT, a radiation oncologist maintains overall responsibility for the patient [17]. In contrast, for the application of STAR, the patient is likely to remain under the primary care of an electrophysiologist, who is responsible for determining whether patients are appropriate for STAR therapy, then identifying and defining arrhythmogenic substrate to target. The electrophysiologist will then work closely with the radiation oncology team to develop a safe and effective treatment plan. The radiation oncology team will then deliver the radiation therapy, with subsequent clinical follow-up with the electrophysiologist for monitoring of treatment efficacy and possible toxicity, and the radiation oncologist for management of radiation-induced toxicities such as esophagitis, bronchial injury, and/or radiation pneumonitis/fibrosis.

Table 1 All reported treatments with STAR to date are tabulated, listing treatment center, underlying VT and cardiac disease etiology, mapping modality, and treatment device and dose

Patient no.	Reference	Treatment center	Cardiac disease etiology and VT source	Mapping modality	Treatment device and dose
1	[12]	Stanford	ICM	Previous EAM or ECG + imaging	CyberKnife
	[14]		Infero-septal, inferior, and infero-lateral walls from base to apex		25 Gy
					90 min
2	[12]	Stanford	Scar	Previous EAM or ECG + imaging	CyberKnife
					25 Gy
3	[12]	Stanford	Idiopathic	Previous EAM or ECG + imaging	CyberKnife
			LV summit		25 Gy
4	[13]	Washington	NICM	ECGI+ imaging	TrueBeam
	[11]		Basal anterolateral LV + basal anteroseptal LV		25 Gy
					51.3 cc
					12 min
5	[13••]	Washington	Mixed ischemic/nonischemic cardiomyopathy	ECGI + imaging	TrueBeam
	[11]				25 Gy
			Anterolateral LV		17.3 cc
					11 min
6	[13••]	Washington	NICM	Previous EAM + ECG + imaging	TrueBeam
	[11]		Inferior posterior lateral LV		25 Gy
					44.5 cc
					14 min
7	[13••]	Washington	NICM	ECGI + imaging	TrueBeam
	[11]		Interventricular septum from inferior wall to outflow tract		25 Gy
					53.0 cc
					12 min
8	[13••]	Washington	ICM	ECGI + imaging	TrueBeam
	[11]		Inferior wall		25 Gy
					81.0 cc
					18 min
9	[15]	Czech Republic	DCM	Previous EAM + imaging	CyberKnife
			Base lateral wall LV		25 Gy
					114 min
10	[16]	Switzerland	DCM	Previous EAM + imaging	CyberKnife
			Interventricular septum		25 Gy
					21 cc
					45 min

Patient Selection

Currently, STAR may be considered when medical or conventional invasive management is ineffective or not possible. Given its noninvasive nature, STAR is particularly well-suited for this population. Additionally, it can be considered in those where endocardial/epicardial ablation cannot access the arrhythmogenic substrate and has been unsuccessful. Its application as primary therapy for patients with VA remains unknown.

Given the early and incomplete state of knowledge regarding risks and benefits of STAR, informed consent must highlight the still experimental nature of this therapy; in particular, the late effects of high-dose radiation to the cardiac sub-structures are still unknown. More recent analyses of patients treated with conventional radiation therapy for lung cancer suggest that major cardiovascular events after RT are more common and have a shorter latency (1–2 years) than previously expected [18–20]. Prior to consideration of therapy, contacting the institution's national regulatory agency and Institutional Review Board (IRB) for guidance may be indicated.

Defining Arrhythmogenic Substrate

Successful ablation, whether through conventional techniques or with STAR, requires accurate identification and localization of the arrhythmogenic substrate. Most typically, this requires a combination of anatomic and electrophysiological identifiers.

EAM can be achieved through catheter-based studies. The maps obtained during electrophysiology studies (EPS) and ablation in patients who have failed prior ablation may be registered to an anatomic image created prior to STAR delivery. An alternative approach is utilizing high-density body surface electrophysiological mapping. There are several technologies available currently that can create three-dimensional activation maps that may help to localize arrhythmia substrate [21•, 22, 23]. In addition to being noninvasive, this technique has the advantage of producing a full electrical map in a single heartbeat, enabling the mapping of hemodynamically unstable VTs [22]. While it has proven effective for epicardial mapping, accuracy beyond the epicardium is unclear [21•, 22, 23].

In patients with SHD, imaging with PET/contrast MRI can identify cardiac scar tissue with arrhythmogenic potential. This is combined with the results of EPS, or perhaps simply a surface 12-lead ECG during VA for localization. There is a growing body of evidence that substrate imaging alone may be appropriate, particularly in ICM [24]. VTs may be unmappable in as many as 65% of patients using current catheter techniques [25, 26]; in many of these cases, hemodynamic instability during attempts at VT entrainment limits mapping [27]. Recurrence of VT in ICM may be due to newly identified VTs from previously non-identified sites. Homogenization of the entire scar region might prevent the rise of future VTs while having minimal impact on LV function as scar tissue is not contractile [24, 28]. As STAR allows delivery of a homogenous, three-dimensional volume of ablative energy in a precise and easily tailored shape, it is uniquely suited to deliver ablation to such VT substrates.

Our recommended approach is to use EAM if possible. In patients with SHD ineligible for catheter studies due to disease state or structural anatomy, PET, contrast MRI can be used to identify the substrate for targeting. The role of noninvasive electroanatomic mapping in substrate identification remains to be defined.

Developing a STAR Treatment Plan

Simulation

The first step of STAR planning is to perform a radiation therapy simulation, which involves immobilizing the patient in a reproducible position for planning and treatment. A CT scan or a respiratory-gated 4D-CT is then performed in order to obtain 3D imaging of the patient in the treatment position. A cardiac-gated 4D-CT or breath-hold fluoroscopy may also provide additional information to account for cardiac motion. Onto these images, the arrhythmogenic substrate for ablation can be defined, and a treatment plan developed detailing how radiotherapy will be delivered to the intended target while minimizing dose to adjacent tissues.

Accounting for Motion

Given the high accuracy of radiation delivery required for STAR, it is vitally important to plan for movement of the intended target. This can be due to movement of the patient as a whole, movement due to respiration, and movement due to the cardiac cycle. Patient body movement is a universal concern in all stereotactic delivery paradigms. Respiratory motion concerns are unique to targets in the thorax and upper abdomen, while cardiac motion concerns impact mediastinal, and in particular cardiac targets. As SBRT has been utilized routinely for pulmonary and upper abdominal targets, but not the heart, respiratory motion compensation techniques have been more developed compared to cardiac motion compensation. However, preclinical studies suggest that cardiac motion accounts for a relatively small displacement of most targets within the heart [29].

There are currently four general approaches to dealing with target movement.

A. Immobilization systems such as vacuum-assisted cushions shape to the patient's body and creates a custom immobilization device. Used both during the simulation and during treatment, this ensures the patient is in the same and limits movement during treatment delivery.
B. Adding a margin (i.e., volumetric expansion to account for error/uncertainty during the treatment planning including internal target motion and patient external motion. This technique helps to ensure the prescribed radiation dose is applied to the intended target, while accepting increased irradiation of surrounding tissues. The clinical target volume (CTV) is defined as the extent of pathologic tissue including microscopic extent and in cardiac cases would refer to the arrhythmogenic tissue. The CTV is expanded to create an internal target volume (ITV), which incorporates respiratory motion using a respiratory-gated 4D-CT to encompass the CTV throughout the respiratory cycle. For cardiac targets, an "ITV_cardiac" is created by utilizing a cardiac-gated 4D-CT of fluoroscopy to delineate the arrhythmogenic substrate throughout the cardiac cycle. The combination of the ITV_cardiac and ITV_respiratory would then produce a margin that accounts for both cardiac and respiratory motion. Lastly, a margin called the PTV (planning target volume) is added to account for any residual uncertainty including calibration of the linear accelerator, resolution and fusion of the various imaging modalities, and

patient movement during treatment, which is typically in the order of 3–5 mm for lung SBRT cases.

C. Gating refers to timing radiation delivery to only one part of the respiratory or cardiac cycle, although cardiac cycle gating has not been clinically validated. This enables smaller margins to be used and subsequently less irradiation of surrounding tissue. However, it increases the duration of the treatment as radiation cannot be continuously delivered.

D. Real-time tracking of the target enables minimum irradiation of surrounding tissues. At present, this can be applied to compensate for respiratory motion with systems such as synchrony respiratory tracking. A metal fiducial marker, in situ from the initial simulation imaging to the completion of treatment, is required for this approach; this refers to a radiologically discrete structure that moves together with the target. Good examples include temporary pacing wires, or PPM/ICD leads. In this technique, the robotically controlled delivery system synchronizes the treatment beam and target zone with the patient's motion in a continuous fashion, based on automated detection and localization of the fiducial marker.

Delivery System

Two X-ray-based delivery systems are currently utilized for STAR, with successful treatments delivered for both: CyberKnife (Accuray, Sunnyvale, CA) and conventional linear accelerators. Conventional linear accelerators include the TrueBeam (Varian, Palo Alto, CA) which has been utilized for STAR and several other systems such as the Axesse (Elekta, Stockholm, Sweden) which have not been utilized for STAR as yet. Technologies utilizing alternative ionizing radiation sources, including proton beams and carbon particles, have varying degrees of clinical use in radiation therapy, and their utility in STAR remains to be determined. Regarding specifically CyberKnife and TrueBeam, the technologies are constantly evolving, with new iterations of each system being released. However, certain fundamental differences remain.

CyberKnife uses a compact linear accelerator which is able to freely move about the patient on a robotic arm. TrueBeam is a gantry-based system which rotates around the patient on a single axis. This enables the CyberKnife system to access more angles for radiation delivery. The CyberKnife system can also be used in conjunction with Synchrony tracking software to enable real-time respiratory motion tracking [30]. With TrueBeam, respiratory motion is compensated with gating [30].

Radiation Dose and Planning

To date, all cases of STAR for VT in humans have used a single dose of 25 Gy. This dose represents a balance of what is deemed safe, yet effective based on preclinical data from several sources. However, data on optimal clinical dose is limited.

Sharma et al. [16] were the first to demonstrate STAR-created cardiac lesions with electrophysiological effect in a porcine model, with 25 Gy the minimum effective dose required. Subsequent studies have supported the effectiveness of 25 Gy in both swine and canines [15]. Others have suggested higher doses; Zei et al. evaluating doses up to 35 Gy [18], Blanck et al. [31] demonstrating 32.5 Gy was required to achieve sufficient fibrosis in swine, and Rafaat et al. [32] testing doses no lower than 35 Gy. The optimal radiation dosing has not been evaluated in detail, including single vs. multiple fractions, and time for delivery of prescribed dose.

The safety of STAR is likely determined by both the prescribed dose and the volume of cardiac tissue targeted. This is an area where research is still lacking. Published national practice and trial guidelines suggest constraining cardiac dose for 1 fraction SBRT to maximum point dose of 22 Gy, and 16 Gy to a volume < 15 mL [33] (Videtic, Hu et al. 2015, Network 2018), very much an approximation. In practice, a dose of 25 Gy has so far been demonstrated safe in both humans and animal models. Despite the lack of knowledge on the radiation dose tolerance of cardiac sub-structures, it remains prudent to incorporate constraints (dose limits) to some of these critical structures. A suggested set of constraints for cardiac SBRT is outlined in Table 2, which can be utilized by the radiotherapy team to optimize the radiation plan [33].

Our Approach

Our approach involves delivery of a single fraction of 25 Gy. We understand that safety and efficacy of dosing either lower or higher than 25 Gy in the clinical setting is still unknown. We have used primarily the CyberKnife system, although LINAC delivery is being evaluated. For CyberKnife delivery, we place a right ventricular septal fiducial marker for real-time tracking to compensate for respiratory motion, in combination with a 3-mm margin to account for cardiac motion. Left ventricular myocardial motion has been demonstrated to be on average up to 4.1 mm [29], a margin of ± 3 mm thus encompasses this. However, it is likely cardiac motion is reduced in patients with SHD. In Fig. 1, a treatment plan for delivery of 25 Gy to the inferior wall of the LV in a patient with VT and ischemic cardiomyopathy is displayed. Isodose curves are shown, demonstrating goal treatment dosing within the target, with rapid falloff of dosing beyond.

Patient Follow-up

Our approach may be divided into two areas—follow-up of procedure efficacy and monitoring for potential side effects. Regarding efficacy, unlike in catheter ablations, immediate

Table 2 Dose constraint recommendations (single fraction)

Tissue	Volume	Max	Endpoint	Reference/notes
Whole heart	Maximum point dose* (excluding PTV)	22Gy	Pericarditis	RTOG 0915
		16Gy	Pericarditis	Videtic et al. [34]
	< 15 cc (excluding PTV)			RTOG 0915
Ventricles	< 1 cc	22Gy	Plan optimization	Estimated constraints
	< 20 cc	16Gy		
Coronary arteries	Maximum point dose*	20Gy	Plan optimization Avoid circumferential dosing for non-occluded/functional coronary arteries	Blanck et al. [35]
Mitral valve	Maximum point dose*	20Gy	Plan optimization	Internal estimate; (EQD2 = 92 Gy)
Papillary muscles	Maximum point dose*	18Gy	Rupture	Internal estimate; (EQD2 = 75.6 Gy)
SA/AV nodes	Maximum point dose*	12Gy	Heart block	Internal conservative estimates based on animal studies at 15 Gy showing 50% partial electrical effect and 50% no effect. [15] **
Other organs at risk				
Spinal cord	Maximum point dose*	14Gy	Myelitis	RTOG 0915
	< 0.35 cc	10Gy		
	< 1.2 cc	7Gy		
Esophagus	Maximum point dose*	15.4Gy	Stenosis/fistula	RTOG 0915
	< 5 cc	11.9Gy	Grade 1 esophagitis	Hergarth et al. [36], Abelson et al. [37], Blanch et al. [35]
	Maximum point dose*	14Gy		
	< 1 cc	9.0Gy		
Trachea and large bronchus	Maximum point dose*	20.2Gy	Stenosis/fistula	RTOG 0915
	< 4 cc	10.5Gy		
Great vessels	Maximum point dose*	37Gy	Aneurysm	RTOG 0915
	< 10 cc	31Gy		
Phrenic nerve	Maximum point dose*	17.5Gy	Neuropathy	RTOG 0915 (extrapolated from brachial plexus)**
	< 3 cc	14		
Stomach	Maximum point dose*	12.4Gy	Ulceration/fistula	RTOG 0915
	< 10 cc	11.2Gy		
Duodenum	Maximum point dose*	16 Gy	Ulceration	RTOG 0915
	< 5 cc	11.2 Gy		
Lung (right and left)	1000 cc	7.4 Gy	Pneumonitis	RTOG 0915
Skin	Maximum point dose*	26 Gy	Ulceration	RTOG 0915
	< 10 cc	23 Gy		

*D0.035 cc

**Limited supporting data

testing for treatment endpoints such as conduction block is not possible. However, ICD interrogation can monitor VA burden, and since cardiac STAR is primarily a palliative treatment, monitoring of patient-reported outcomes and symptoms of VA will provide valuable additional data on treatment efficacy. Additionally, it is important to consider the delayed development of the electrophysiological effects of STAR, and as such follow-up should be over a greater duration.

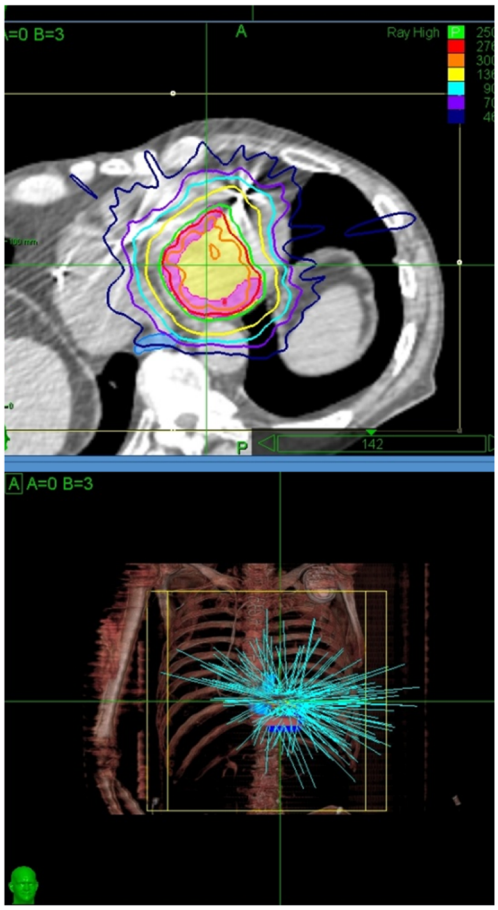

Fig. 1 Treatment planning for delivery of 25 Gy to the inferior LV of a patient with VT and ischemic cardiomyopathy. Note the isodose curves demonstrating goal treatment dose within the target, with rapid falloff beyond. The planned delivery beams are also displayed

Safety monitoring involves a combination of patient-reported symptoms and imaging to monitor for both cardiac and extracardiac side effects. We recommend echocardiography and CT to assess for pericardial disease, myocardial dysfunction, valvular disease, coronary artery disease, and lung injury and close clinical follow-up to assess and manage radiation-related toxicities such as esophageal injury and/or radiation pneumonitis. However, to date, no such complications have been reported.

Future Developments

A Truly Noninvasive Procedure

For STAR to be a completely noninvasive process, identification of arrhythmogenic substrate must also be noninvasive. Imaging modalities which enable identification of myocardial scar, surface body mapping holds promise, but the accuracy and applicability of these technologies are not yet validated.

The Treatment of Other Arrhythmias

While VT has been the target in the majority of STAR ablations to date, it has also been utilized in atrial fibrillation [38] Theoretically, the technique of STAR could provide a noninvasive alternative to any traditional catheter ablation.

Radiation Type, Dose, and Safety

To date, all human cases of STAR have used traditional photon beam therapy. However, in the oncological field, there is increasing use and development of alternative strategies, including MR-guided SBRT (Fischer-Valuck, Henke et al. 2017) and use of particle-based techniques of proton and carbon ion radiotherapy. Lehmann et al. [39, 40] have described the use of carbon ion particle therapy for STAR in a porcine model. How these newer techniques will impact the development of STAR is yet to be determined.

Regarding dose, all STAR procedures have used 25 Gy. Recurrence of VT has occurred in some patients. Whether this is due to new VT circuits developing or re-activation of the original arrhythmogenic substrate is not clear. However, if the latter is the case, higher doses may offer a solution [9••, 12].

Mechanism of Cell Death

Greater understanding of the underlying mechanisms by which STAR causes cell death may improve dose titration. Fibrosis and scar formation is required to disrupt an arrhythmogenic circuit. Traditional catheter ablation uses radiofrequency energy to heat tissue, leading to cell necrosis. However, the mechanism by which high-dose radiotherapy causes cell necrosis is poorly understood, particularly in non-cancerous cells.

One possible explanation involves a combination of vascular injury which subsequently leads to tissue hypoxia, and apoptotic cell death following double-strand breaks in DNA [1, 41]. In animal studies, histopathological examination has consistently demonstrated dose-dependent fibrosis, fatty tissue necrosis, and loss of cellular organization [15, 16, 31, 32]. Additionally, intramyocardial vessels have been shown to demonstrate severe vasculitis with fibrinoid necrosis, medial destruction, and luminal thrombi [15].

These progressive changes take time to develop over upwards of 2 months, and animal studies support this hypothesis based on electrophysiological observations 15, 16, 31, 32. However, human studies have demonstrated an improvement in arrhythmia burden after days not months [9••, 13••, 14], [42]. The mechanism of this acute benefit remains to be elucidated, but may involve an acute inflammatory response.

Conclusions

Early use of STAR for the treatment of VT has shown great promise. Initial cases have paved the way to it becoming a viable treatment option in those where traditional methods have failed. However, in order for STAR to be utilized as first-line therapy for VT, ablation target planning cannot rely on prior invasive electroanatomic mapping. Surface mapping techniques may help achieve this end, as might the further evaluation of a purely anatomic substrate-based ablation strategy. Future trials, both clinical and pre-clinical, will further our knowledge of the efficacy and safety of STAR, enabling us to develop more refined protocols for its application.

Compliance with Ethical Standards

Conflict of Interest Dr. Sharp has nothing to disclose.

Dr. Mak reports personal fees from AstraZeneca and personal fees from New RT, outside the submitted work.

Dr. Zei reports grants and personal fees from Cyberheart, Inc., grants and personal fees from Biosense Webster, Inc., and personal fees from Abbott/St Jude Medical, Inc., during the conduct of the study.

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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