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Stereotactic Body Radiotherapy for Noninvasive Arrhythmia Treatment

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ABSTRACT

Atrial fibrillation (AF) is the most common cardiac arrhythmia clinically and a major risk factor for cardiogenic stroke, especially in the elderly, and also one of the factors leading to heart dysfunction. Conventional treatment methods for restoring sinus rhythm include synchronous electrical cardioversion, pharmacological cardioversion and radiofrequency ablation, which are effective but still limited due to treatment failures to control sinus rhythm and the side effects of long-term medication and the invasiveness of radiofrequency ablation. Ventricular tachycardia (VT) is a malignant arrhythmia, which is the most common cause of sudden cardiac death (SCD). Antiarrhythmic medications and endocardial catheter ablation remain as guidelines-supported VT treatment strategies for patients with structural cardiac abnormalities. Recent clinical results showed that more than half of patients had recurrent VT after catheter ablation, and for patients with intracardiac thrombosis, deep ablation sites, or mechanical valve replacement, catheter ablation is often not completed. The invasive and potential complications of radiofrequency ablation make it unattractive for patients with multiple complications or hemodynamic impairments. This paper describes the stereotactic body radiotherapy (SBRT) technique and its clinical potential for the noninvasive ablative treatment of AF and VT together with its important implications for future beneficial clinical applications. In vivo experimental studies that provided useful preclinical data are reviewed and the results of pioneering clinical trials will be discussed together with the dosimetric considerations and pros and cons of the treatment approach.

Keywords: Ventricular tachycardia, Atrial fibrillation, Stereotactic body radiation therapy (SBRT), Ablation, Non-invasive treatment

BACKGROUND

Atrial fibrillation (AF) is the most common cardiac arrhythmia clinically. Its morbidity increases with age and represents 1% in people over 60 years of age [1]. Atrial fibrillation is a major risk factor for cardiogenic stroke, especially in the elderly [2], and is also one of the factors leading to heart dysfunction. It has a significant negative impact on quality of life,

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and increases the risk of death. Studies found that patients with AF had a mortality rate 1.5 to 1.9 times higher than those without AF [3]. The pathogenesis of AF is very complex. It is a highly heterogeneous and complex disease with a varying pathogenesis in different patients [4-8]. However, histological studies have shown that AF is a disease of the posterior wall of the left atrium (LA). Atrial fibrillation most often originates in the pulmonary veins. Atrial fibrillation can be caused by ectopic electrical activity of the muscle sleeve around the vein, and reentry conduction in the muscle sleeve helps maintain AF [5,9]. The goals of AF treatment include restoring sinus rhythm as much as possible, reducing symptoms, preventing stroke, and preventing cardiomyopathy associated with tachycardia [10]. Evidence-based trials have shown that patients with a recovered sinus rhythm did not benefit more than those with controlled ventricular rate. For most patients with AF, rhythm control is no longer the preferred strategy. However, these trials did not include young patients or patients with highly symptomatic AF [11-14]. Therefore, rhythm control in these patients is reasonable. Current treatment methods for restoring sinus rhythm include synchronous electrical cardioversion, pharmacological cardioversion and radiofrequency ablation. Catheter ablation techniques essentially depend on the mechanism of this arrhythmia. The most common ablation method for atrial fibrillation is the circumferential LA ablation strategy, which includes ablation lines in the left posterior atrium and the mitral valve isthmus. Recent studies have confirmed the presence of vagus nerve fibers and/or ganglia around PV ostia at the venoatrial junction. Usually, LA lesions need to ablate AF with the vagus innervation area. CPVA eliminates triggers and stroma including local vagal denervation [15]. This helps prevent recurrence of AF after treatment. The radiofrequency surgical ablation at times can be complicated, and a certain percentage of surgical failures exist. In addition, a considerable number of patients have AF recurrence after treatment with drugs and radiofrequency ablation. It is difficult to maintain sinus rhythm, which is also coupled with side effects of long-term drug treatment and the invasiveness of radiofrequency ablation. Thus, the application of both methods is limited. Therefore, the effort to develop better cardioversion methods to control sinus rhythm is imperative.

Ventricular tachycardia (VT) is a malignant arrhythmia, which is the most common cause of sudden cardiac death (SCD), currently. Approximately 300,000 to 400,000 people die each year from heart attacks in the United States. It has attracted widespread social attention [16,17]. Ventricular arrhythmia can usually occur in fibrous structural heart disease, cardiac channel disease, often caused by myocardial ischemia, myocardial infarction or non-ischemic disease, and it can also occur in a normal heart [18]. Types include scar-related ventricular tachycardia, bundle branch reentry ventricular tachycardia, Hebund's bundle Purkinje fiber-related VT, papillary muscle-related VT, epicardial VT and other unexplained VT. Scar-related VT is avital cause of sudden death and morbidity in patients with heart disease. Myocardial infarction, or replacement fibrosis in nonischemic cardiomyopathies is a common source of scarring. Ventricular scars consist of fibrotic areas dense with collagen and fibroblasts, but also contain areas of surviving muscle cell bundles [19,20]. The dense fibrosis causes conduction blocks to define the boundaries of the reentry circuit. Fibrosis also helps produce slow conduction that requires reentry. At the microscopic level, fibrosis separates myocyte bundles, forcing the excitation wavefront to take a circuitous course through the bundles. In addition, cell-to-cell conductivity is reduced, this uncoupling of myocyte bundles and to some extent the myocytes within the bundles slows conduction, although action potentials and ion channels in the myocytes can be relatively normal. Slow conduction and fibrous anatomic barriers set the stage for reentry. This is the main mechanism of scar VT, which can be cured by radiofrequency ablation. The main targets of VT management are the reduction of SCD risk and the improvement of overall survival. Antiarrhythmic medications and endocardial catheter ablation remain as guidelines-supporting VT treatment strategies for patients with structural cardiac abnormalities, and an implantable cardioverter defibrillator (ICD) is usually required [21]. ICD positively protects patients, but at times, it cannot optimally control VT. A recent trial showed that more than half of the patients had recurrent VT after catheter ablation [22]. In addition, for patients after mechanical valve replacement or patients with intracardiac thrombosis or deep ablation sites, catheter ablation is often not completed. The invasive and potential complications of radiofrequency ablation make it unattractive for patients with multiple complications or hemodynamic impairments. Should a relatively non-invasive method be proven safe and effective, then it would be an option, especially for those patients who cannot tolerate the radiofrequency ablation treatment due to cachexia or severe heart failure.

In this review paper, recent advances in stereotactic body radiation therapy (SBRT) for noninvasive ablative treatment of AF and VT are reviewed together with their important

implications for future beneficial clinical applications. We also discuss the dosimetric considerations of SBRT for AF and VT and the pros and cons of the treatment approach.

The SBRT technique and image guidance

Stereotactic body radiation therapy is a well-established radiation oncology ablation technique (external beam radiation therapy that uses x-rays or gamma rays to irradiate target tissues). It is used to deliver high doses of radiation to targets in the body in a few treatment fractions (e.g., hypofractionated radiotherapy). With advanced image guidance techniques, SBRT can deliver highly conformal dose distributions accurately to predetermined targets while minimizing doses to adjacent normal anatomic structures [23]. The images used in SBRT are critical to the entire process. 2D or 3D x-ray imaging techniques and, recently, MR imaging have been used for SBRT. Respiratory tracking and control techniques have also been developed for targets that are affected by respiratory motion, e.g., respiratory gating, tumor tracking, organ motion dampening, or patient-directed or patient-mediated methods [23,24]. Treatment time varies from a few minutes to a few hours depending on the treatment machine, delivery technique, prescription, target size and location. Treatment is noninvasive and painless without the need for sedation [25]. It is typically a noninvasive treatment that has been shown to be safe and effective for cancer patients who have failed other treatment modalities. SBRT is mainly used to treat malignant tumors and some benign diseases. For example, arteriovenous malformations, trigeminal neuralgia, auditory neuromas, and meningiomas are often accepted as segmented external beam stereotactic radiosurgery. Recently, this technology has been evaluated for treatment of a limited number of patients with malignant arrhythmias, including AF and VT with favorable results.

Application of SBRT for atrial fibrillation

In recent years, SBRT has gained favor in treating AF, although most treatments involve animal tests. In an early 2009 study, for example, Sharma et al. mapped the LA and successfully ablated sixteen Hanford-Sinclair mini swine [26]. Their results showed that a radiation dose of 25 Gy was needed to produce an electrophysiologic effect. It was feasible to produce a bidirectional cavotricuspid isthmus block and AV nodal conduction block. The pulmonary vein–LA junction and LA appendage showed marked voltage reduction to less than 0.05 mV. No spontaneous arrhythmias were observed. Pathological specimens showed no evidence of radiation damage outside the target. Histology samples from target sites showed effects consistent with X-beam radiation [26].

In 2014, Bode et al. performed electrophysiological voltage mapping in the LA and the upper right PV in 8 adult Goettingen mini-pigs [27]. Radiation was delivered with a conventional linear accelerator. A single homogeneous dose ranging from 22.5 to 40 Gy was applied circumferentially to the target vein antrum. It was shown that complete block of atrio-venous electrical conduction occurred after 40 Gy dose irradiation. The results indicated that pulmonary vein isolation to treat AF can be achieved by radiosurgery with a conventional linear accelerator. Yet, it requires a high radiation dose, which might limit its clinical applicability [27].

More recently, Lehmann et al. investigated the effect of extracorporeal photon radiation on catheter-free ablation of normal pig atrioventricular nodes [28]. They concluded that single-fraction doses as low as 25 Gy could cause a lesion with interruption of cardiac impulse propagation using this respective target volume. With doses of ≤55 Gy, maximal point-doses to coronary arteries could be kept under 7Gy, but target conformity of lesions was not fully achieved using this approach [28].

To assess the safety and effectiveness of stereotactic radioablation, Zei et al. studied the targeting accuracy for pulmonary vein tissues in an experimental model with 17 adult canines and 2 adult swine [29]. Four treatment doses (15, 20, 25, and 35 Gy) were administered to 4 cohorts. Subjects were monitored for 3–6 months, followed by electrophysiological testing, gross pathological examination, and histopathology in 2 subjects. SBRT treatment plans were generated to deliver planned doses accurately in the LA and upper right PV. They concluded that SBRT is safe and effective for creating precise circumferential scar and electrical isolation of the right superior PV in an experimental model, showing clear dose dependence of the observed electrical effects [29].

Based on the preclinical data obtained from the above in vivo animal experiments, pioneering clinical treatments were designed for the treatment of AF using stereotactic radio ablation, and the initial results were reported by Qian et al. in 2017 [30]. Two patients with paroxysmal AF, who failed medication and refused radiofrequency ablation, were selected for this study. The SBRT method was used to isolate the pulmonary vein from the posterior wall of the LA. The patients were treated in an ambulatory setting without interruption of antiarrhythmic medications or anticoagulation. Clinical follow-up was performed through

at least 24 months after therapy. It was found that SBRT was successfully planned and treated in both patients, and no obvious early or long-term side effects occurred during 48 months of follow-up. One patient had AF recurrence after 6 months without arrhythmia, while the other patient had AF recurrence after 24 months. Fibrosis on MRI scans was consistent with radio ablation.

Table 1: SBRT dosimetric parameters for the treatment of atrial fibrillation [30].

	Patient 1	Patient 2
Prescription dose (Gy)	25 Gy	25 Gy
Collimator size (mm)	Fixed 20 mm	Fixed 7.5 mm, 12.5 mm, and 20 mm.
Beams	241	269
Monitor Units (MU)	44 665	48 303
Treatment volume (ml)	48.87	54.5 ml
Mean delivered dose to target and nearby tissues (range)		
Targeted left atrial myocardium	35.21 (14.27-35.21) Gy	34.24 (16.99-34.25) Gy
Untargeted myocardium	12.62 (1.22-35.18) Gy	9.52 (1.93-34.25) Gy
Mitral valve	18.53 (15.06-22.93) Gy	10.87 (5.88-20.58) Gy
Pericardium	11.19 (1.19-35.18) Gy	7.31 (1.90-32.71) Gy
Lung	3.93 (1.00-30.94) Gy	3.52 (1.45-18.04) Gy
Esophagus	5.54 (1.18-16.65) Gy	4.61 (1.81-15.04) Gy
Spinal cord	3.25 (1.16-9.67) Gy	3.95 (1.71-6.62) Gy
Treatment time (min)	90	90

The study showed the feasibility to deliver SBRT for a complex lesion set to LA. Their treatment procedure requires advanced image-guidance for precise target localization and accurate delivery of ablative dose distributions. To improve target tracking during cardiorespiratory motion, an internal fiducial marker was placed transvenously in proximity to the LA target, specifically at the right atrial septum. Under fluoroscopic guidance, an active fixation unipolar pacing lead was placed in the right atrium and attached to the interatrial septum via right internal jugular vein vascular access obtained using the Seldinger technique (Figure 1). This ensures that no specific movement or breathing restrictions were required of the patient during treatment. The patient was placed in a supine position and a planning contrast-enhanced cardiac computed tomography (CT) of the LA was performed. A three-dimensional (3D) rendering of the LA was created using cardiac-specific contouring software to identify the treatment target. An SBRT treatment plan was developed for the CyberKnife system using Multiplan treatment planning software (Accuray Inc., Sunnyvale, CA). The treatment plan was designed to ensure that >25 Gy of therapeutic radiation was delivered to the intended target without exceeding the maximum dose of 35 Gy (Figures 2 and 3). Real-time imaging with planar x-rays was utilized to localize the treatment target using a fiducial marker as guidance. The SBRT treatment lasted approximately 90 minutes (Table 1). No procedural sedation was required. The fiducial marker was removed immediately after SBRT treatment, and the patient was discharged home.

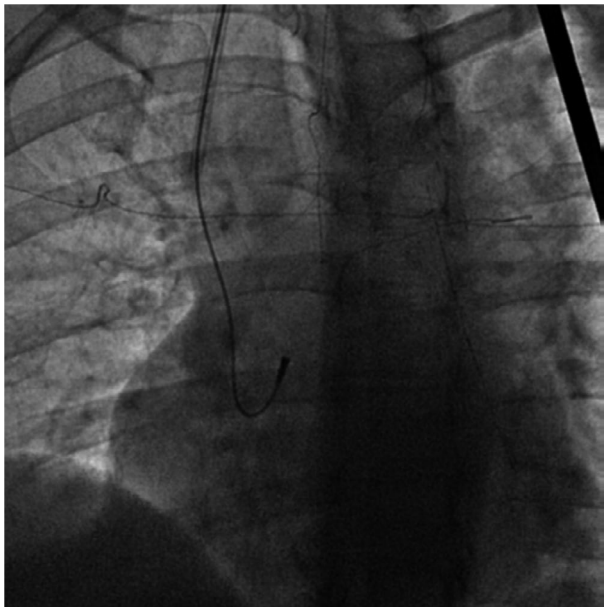

Figure 1. Placement of an internal fiducial marker to improve the accuracy of SBRT treatment. This fluoroscopic image shows the position of the fiducial marker placed via right internal jugular vein access, and affixed to the right side of the interatrial septum, in close proximity to the LA target. Compensation for cardiorespiratory motion during SBRT is achieved by the external beam delivery system through tracking of fiducial movement using planar x-ray imaging [30].

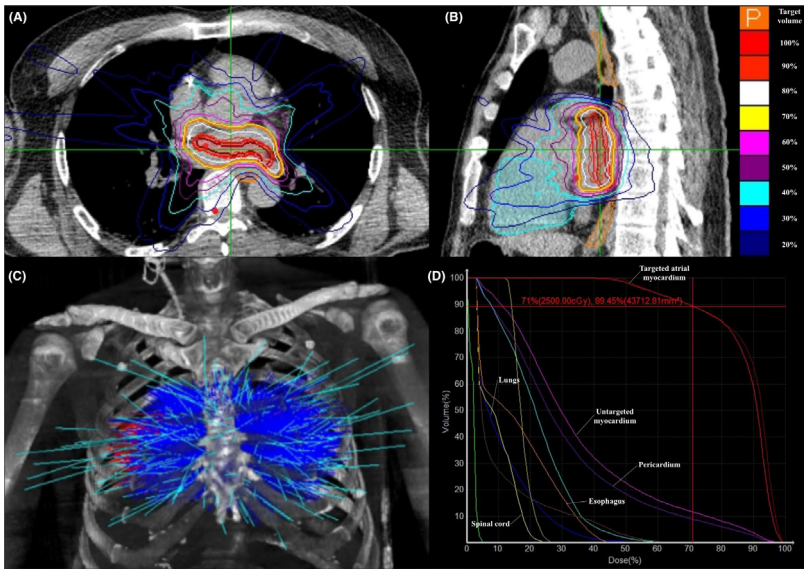

Figure 2. Planning and delivering stereotactic radioablation to the LA (patient 1): panels A and B show transverse and sagittal CT images through the LA demonstrating radioablative isodose contours within and around the planned treatment volume defined by the orange line. Panel C demonstrates the calculated multiple beam angles used to deliver a conformal dose distribution to the treatment volume. Panel D shows the proportion of dose delivered to the targeted atrial myocardium and other nearby visceral tissue volumes; it can be seen that approximately 89% of the target volume received at least 25 Gy [30].

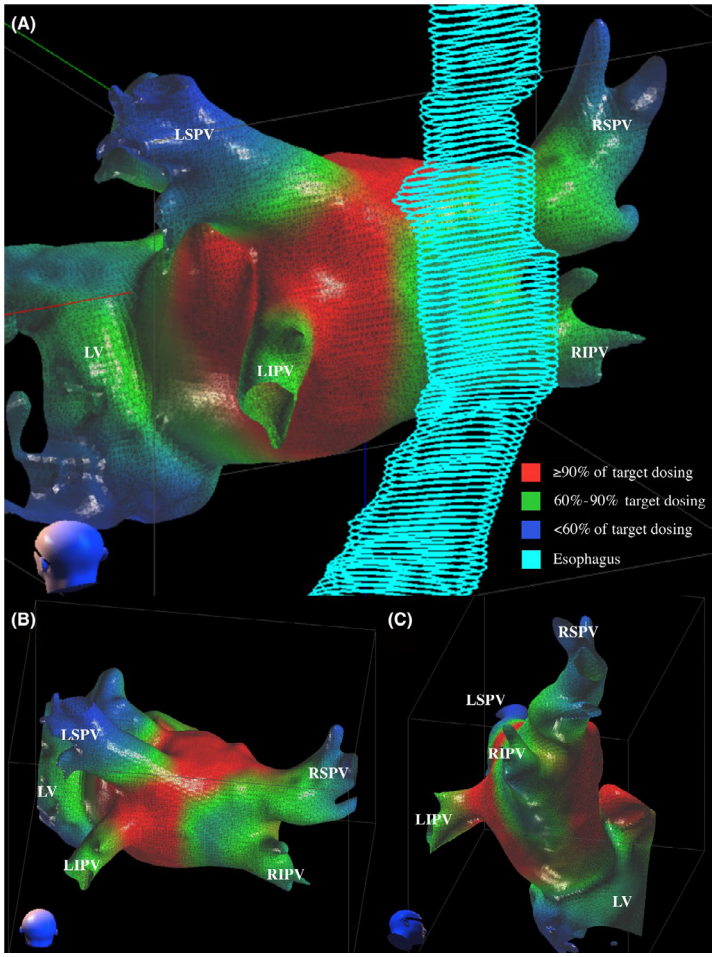

Figure 3. Anatomical considerations in tailoring the radioablative lesion set. Treatment dosing for Patient 2 is displayed on the 3D LA volume using the SBRT treatment planning software. Panel A shows a posterior-anterior projection of the LA with the esophagus in situ to demonstrate the arrangement of the lesion set to minimize esophageal dosing. Panels B and C are additional posterior-anterior and right lateral caudal views with the esophagus removed. Red signifies dosing at or above 90%, green (60%-90%) and blue (<60%) of the target prescription dose of 25 Gy. LSPV: Left superior pulmonary vein; LIPV: left inferior pulmonary vein; RSPV: right superior pulmonary vein, RIPV: right inferior pulmonary vein; LV: left ventricle [30].

Currently, only a small number of patients received this treatment with limited observations. More clinical experience will be needed in the future to better understand the effectiveness and safety of this treatment model. Further research is needed in a larger patient population to determine whether pulmonary vein isolation is feasible and to observe the cardiotoxicity of radiation to consider whether this treatment is beneficial.

Application of SBRT for ventricular tachycardia

Myocardial scars from infarction or replacement fibrosis in nonischemic cardiomyopathies are the common substrate for sustained monomorphic VT [31]. Although radiofrequency (RF) ablation remains the gold standard for the treatment of drug-refractory VT, the outcomes are less than ideal, especially in the nonischemic cardiomyopathy population. Stereotactic body radiation therapy (SBRT) has been shown to be effective in treating patients with refractory VT because of scarring [32]. Case studies from multiple centers have suggested the efficacy of catheter-free, electrophysiology-guided noninvasive cardiac radioablation for scar-related VT using the SBRT technique [33-37]. Clinical outcomes of SBRT for VT have been reported in case studies. These investigations have been carried out in multiple research centers. This treatment is mainly for patients with structural heart disease, most with an ICD; patients who have undergone conventional treatments with poor efficacy; and, patients with refractory VT who have had

recurrent attacks, e.g., ICD-treated VT at least three times in three months, despite taking at least two antiarrhythmic drugs, and having undergone at least one catheter ablation treatment [34].

Loo et al. reported for the first patient treated with SBRT for AAD-refractory VT after myocardial infarction in 2015 [38]. The VT substrate was made of surviving myocardial fibers within the scar according to the PET-CT. Scar-related electrophysiology and definition of critical areas involved in re-entrant arrhythmias was obtained by invasive electro-anatomical mapping during VT, induced by their implanted cardioverter-defibrillator prior to catheter based ablation. This can be done prior to radiotherapy, and the target defined by mapping can be used to construct the target volume for radiotherapy. The treatment was delivered with the CyberKnife radiosurgery system and a temporary pacing wire placed at the right ventricular apex to ensure accuracy (i.e., function as fiducial marker). A plan using high-energy photons in a single 25-Gy dose to a target region of human ventricular myocardium was designed along with a maximum dose of 33 Gy concentrated to the extensive scar region. In the first two months after the treatment, the VT episodes logged by the ICD interrogations dropped significantly to 52 episodes per month from the 562 episodes before the SBRT treatment. Meanwhile, no definite acute or late complications were found in the prognostic treatment regimen. With a stable antiarrhythmic regimen, the reduction of VT episodes was maintained for seven months. Then, with the recovery of the arrhythmia substrate, the COPD and recurrent VT occurred. The case confirmed the effectiveness of the SBRT treatment. The assumption was made which hypothesized that a larger radiation dose can improve the durability of the treatment.

Another pioneering experience with a small series investigation was reported by Cuculich et al. in 2017 [34]. Outcomes of this study for the treatment of VT in 5 patients were excellent and were bolstered by a subsequent larger prospective analysis based on 19 patients [33], in which the efficacy of SBRT was well substantiated. The treatment procedure was similar to that for their first 5 patients [34] including mapping of the VT substrate, dose prescription (25 Gy) and delivery technique. Preliminary results of this trial with a median follow-up of 13 months were published by Robinson et al. [33] showing remarkable efficacy in VT burden reduction. The VT burden and modest short-term risks were significantly reduced. A strong VT burden reduction of 99.9% was observed after a 6-week blanking period, allowing patients to reduce their antiarrhythmic drug use. Although no fiducial or tracking techniques were used to improve the localization accuracy for the VT substrate, a completely non-invasive mapping method was used combining a chest CT with a high density surface electrocardiographic imaging technique (ECG-vest with 256 electrodes that targeted the exit site of the VT and the surrounding ischemic substrate (i.e., infarction and its border zone). The patients received 25 Gy in a single fraction (mean target volume of 49 cc) delivered using a clinical linear accelerator dedicated for SBRT. There were no acute procedural toxicities. Regarding toxicity, 2 patients (10.5%) experienced grade 3 treatment-related adverse events (heart failure and pericarditis) within 90 days of SBRT delivery. In addition, six patients (28%) had treatment-related pericardial effusions including one grade 3 and one grade 4 and 11% of patients had pneumonitis that resolved with steroids. The authors recently presented longer-term results showing a persistent effect of SBRT, 2 years after treatment in most patients. Additionally, serious toxicity was low, but could occur after 2 years: two grade 3 pericardial effusions, one grade 4 gastro-pericardial fistula and no adverse effects in the ICD systems. After the treatment, patients reported a markedly improved health-related optimism in the quality-of-life survey, indicating a confidence boost with the reduced VT episodes.

Furthermore, Neuwirth et al. published a larger retrospective case series on SBRT in VT patients who were refractory to previous catheter ablation with longer term follow-up in 2019 [39]. Mapping of the VT substrate was based on an electrophysiological (EP) study using an EAM system (CARTO3, Biosense Webster, Israel) for their first patient and SBRT was delivered using the Cyber Knife radiosurgery system with a single fraction of 25 Gy (mean PTV of 22.2 cc). Results of this series have been recently published at a median follow-up of 28 months. Ten patients were treated, with a VT burden reduction of 87.5% compared to baseline; however, after a 3-month blanking period, VT recurred in 8/10 patients. Finally, they reported one possible treatment-related toxicity (mild nausea) and a possible grade 3 late treatment related toxicity (progression of mitral regurgitation 17 months after SBRT). To further study the long-term safety and efficacy of SBRT for VT, the authors have initiated a multicenter prospective study (NCT03819504).

In 2019 Robinson et al. published a similar article. They conducted a prospective phase I/II trial of noninvasive cardiac radioablation in adults with treatment-refractory episodes of VT or cardiomyopathy related to premature ventricular

contractions (PVCs) for 19 patients [33]. Arrhythmogenic scar regions were targeted by combining noninvasive anatomic and electric cardiac imaging with a standard stereotactic body radiation therapy workflow followed by delivery of a single fraction of 25 Gy to the target. The primary safety end point was treatment-related serious adverse events in the first 90 days. The primary efficacy end point was any reduction in VT episodes (tracked by indwelling implantable cardioverter defibrillators) or any reduction in PVC burden (as measured by a 24-hour Holter monitor) comparing the 6 months before and after treatment (with a 6-week blanking window after treatment). Health-related quality of life was assessed using the Short Form-36 questionnaire. The final conclusion showed in patients with intractable VT, the use of electrophysiology-guided noninvasive stereotactic cardiac radiotherapy was associated with a marked reduction in the burden of VT with reduced antiarrhythmic medication use and improved quality of life.

Similar results can also be found in the report of Jumeau et al.[40]. They performed the first SBRT in rescue treatment for an intensive care patient, which effectively prevented the electrical storm in the following 4 months. They also found an immediate reduction in VT episodes after the treatment, suggesting there are other mechanisms except the radiation-induced fibrosis.

Lloyd et al. reported their clinical experience in a series of critically ill advanced heart failure patients who underwent SBRT as a compassionate use option for the treatment of refractory VT and VF [32]. Due to the relatively short and noninvasive nature of the treatment, this therapy holds promise for advanced heart failure patients who have exhausted all other options but continue to experience recurrent VT and ICD therapies. In their study, SBRT showed an acute safety for these critically ill patients with no serious adverse reactions. The reduction rate of VT burden in total was 69% and 94% after the exclusion of a single outlier, which is well below the results reported by others. The reason may be the lack of the 3-dimensional mapping of the real-time induced VT used in the previous study. This is due to the critically ill condition of the patient in which such a method is no feasible. Another finding of their study is the relatively short effective time unlike previous reports. Endothelial vacuolization and disruption of gap junctions were found in the histology observed during transplantation, which contributes to the shorter effective time.

CONCLUSION

Stereotactic radiation therapy is an alternative treatment model, which has great potential to become a safe and effective method for treating arrhythmias. The direct appeal of non-invasive SBRT for VT ablation implies that it is suitable for a wider patient population, especially patients with severe illness, severe left ventricular dysfunction, and VT patients who do not benefit from current methods. In addition to the treatment of cardiac arrhythmia substrates, stereotactic ablation can potentially be applied to therapy for other cardiac and non-cardiac targets. Septal ablation for the treatment of LV outflow obstruction associated with hypertrophic cardiomyopathy, denervation of autonomic cardiac input for incessant VT, long QT syndromes, or catecholaminergic polymorphic ventricular tachycardia (CPVT) may be useful. Stellate ganglionic plexus ablation or renal autonomic denervation for hypertension may also be potential targets with this treatment technique.

Given the early stages of evaluation of this technology, the long-term toxic effect of radiotherapy on cardiac structures has not been fully confirmed. At present, experimental data are limited. Only a single treatment dosing regimen, namely, 25 Gy in a single fraction, has been utilized and evaluated. This particular regimen is based on prior reported treatments [38]. In addition to the demonstration of efficacy, dose-finding studies have defined ranges of effective therapy delivery and toxicity thresholds. Importantly, no radioablative treatment-related complications were seen both with clinical and pathologic/histologic evaluation in treatments up to 35 Gy. Based on these data, as well as SBRT experiences in the oncology literature, 25 Gy as a single dose has been used in nearly all clinical treatments, even though higher dosing was found to be safe in preclinical studies. At this time, the optimal dose in humans remains undefined [34] and additional research and clinical studies are needed. Current preclinical and clinical experience indicates early efficacy and safety. Advanced clinical trials are warranted to fully evaluate its safety and efficacy in larger populations of patients.

Though the promising efficacy on suppressing VT has been described, SBRT still has a long journey before becoming a promoted therapy. Minimizing the irradiation on surrounding tissues is still an essential task for SBRT and requires a more accurate minimal dose for the effective treatment in order to reduce the dose on the surrounding tissue and avoid long-term complications. More advanced target definition and tracking technology is also needed

for the guidance of stereotactic radiotherapy. A new type of particle beam treatment, such as protons and carbon ions, is also an emerging technique with a promising efficacy [41].

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