Cardiac stereotactic radiotherapy for refractory ventricular tachycardia in a patient with wireless left ventricular endocardial stimulation system

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Introduction

Cardiac stereotactic body radiotherapy (SBRT) is a novel therapy for refractory ventricular tachycardia (VT). The WiSE CRT (Wireless Stimulation Endocardially for Cardiac Resynchronization Therapy; EBR Systems, Sunnyvale, CA) is a promising method of left ventricular (LV) resynchronization using a leadless implanted LV device in conjunction with a right ventricular pacing system. We present the first report of successful cardiac SBRT delivered safely in a patient with WiSE CRT.

Case report

An 83-year-old man had a history of coronary artery disease, ischemic cardiomyopathy with LV apical infarct and LV ejection fraction (LVEF) 35%, chronic NYHA class III heart failure status post cardiac resynchronization therapy (CRT) defibrillator placement, recurrent VT, underlying left bundle branch block, paroxysmal atrial fibrillation, and chronic kidney disease. He had multiple presentations with sustained VT requiring implantable cardioverter-defibrillator (ICD) shocks, which continued despite amiodarone and mexiletine. He underwent endocardial LV catheter mapping/ablation with Navistar (Biosense Webster, Irvine, CA) remote magnetic navigation catheter. Substrate map showed moderate-sized apical infarct (Figure 1A). Activation mapping–guided radiofrequency ablation was performed, terminating the clinical VT originating from the apical low-voltage region. This was complicated by pericardial effusion requiring emergent pericardiocentesis but no surgical intervention. Amiodarone was discontinued during follow-up owing to subjective adverse effects and he remained on mexiletine.

KEY TEACHING POINTS

- Cardiac stereotactic body radiotherapy (SBRT) is a salvage option for refractory ventricular tachycardia with structural heart disease.
- WiSE-CRT (Wireless Stimulation Endocardially for Cardiac Resynchronization Therapy; EBR Systems, Sunnyvale, CA) is a promising leadless left ventricular endocardial pacing modality for cardiac resynchronization therapy.
- We present a proof-of-concept case of successful cardiac SBRT in a patient with WiSE CRT.
- In presence of cardiac implantable electronic device (CIED), especially WiSE CRT with device electronics in close proximity to the ventricular myocardium, careful SBRT treatment planning is needed to minimize radiation dose delivered to the CIED.
- Cardiac SBRT in presence of CIED is considered high risk for radiation interaction and device malfunction and requires continuous patient monitoring, including video surveillance, pulse oximetry, and continuous electrocardiogram telemetry.

A year later, he had elevated LV impedance and capture thresholds with loss of LV pacing and worsening heart failure. LVEF had declined to 20%. As part of the SOLVE CRT trial (Stimulation Of the Left Ventricular Endocardium for Cardiac Resynchronization Therapy in Non-Responders and Previously Untreatable Patients), he underwent WiSE CRT implant.

For recurrent VT episodes, sotalol was added to mexiletine. Unfortunately, he was rehospitalized a month later for VT storm with device-logged 59 episodes of VT and multiple

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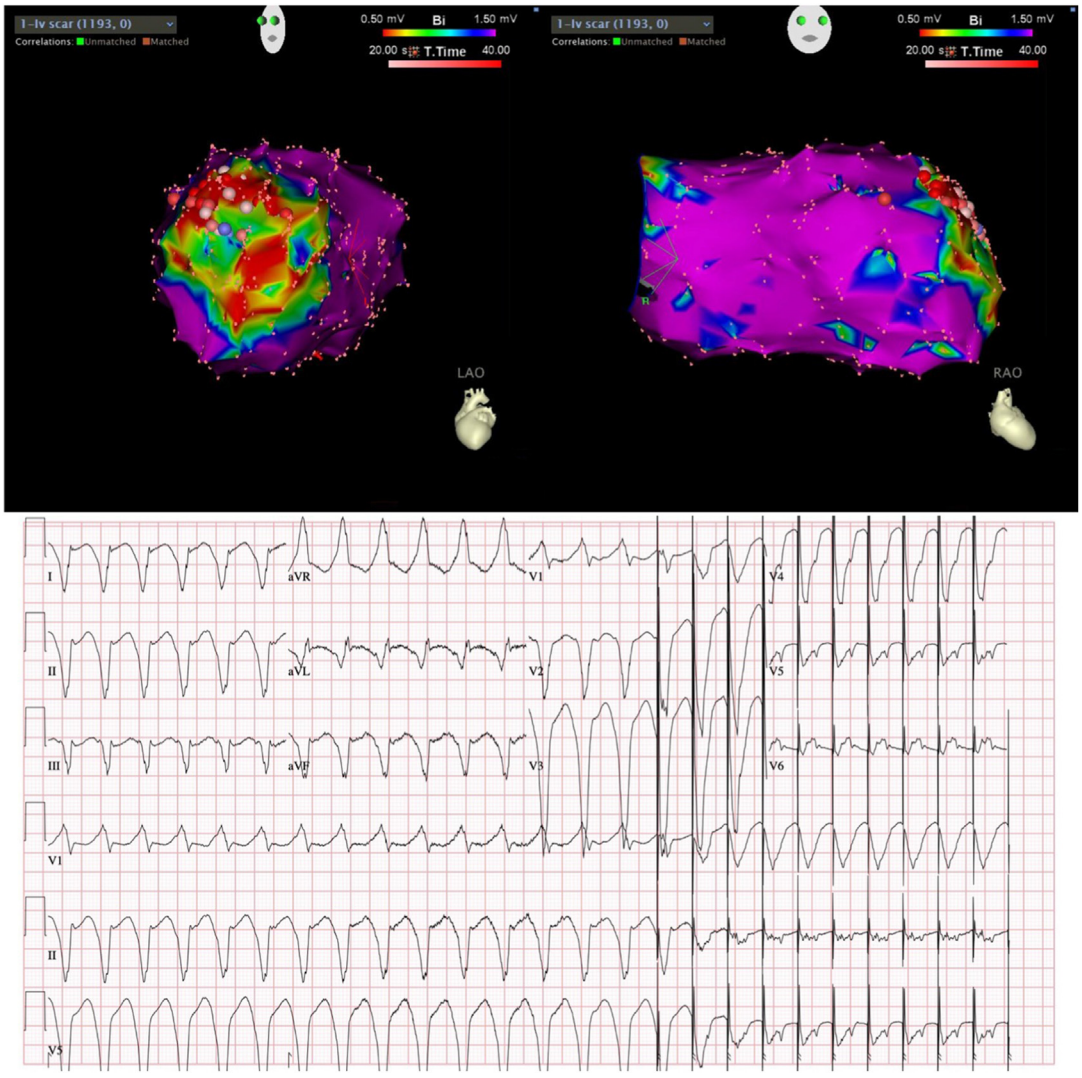

Figure 1 **Top panel:** Voltage maps from the patient's prior catheter ablation performed for recurrent ventricular tachycardia showing the left ventricular apical scar in left anterior oblique (LAO) and right anterior oblique (RAO) views. **Bottom panel:** A 12-lead electrocardiogram of the patient's ventricular tachycardia being treated with antitachycardia pacing from his implantable cardioverter-defibrillator.

antitachycardia pacing (ATP) therapies without ICD shocks. He declined repeat catheter ablation. Sotalol was switched to amiodarone and evaluation for cardiac SBRT was initiated. He was readmitted a week later with incessant VT ~133 beats per minute and 204 episodes of ATP-terminated VT (Figure 1B) despite amiodarone and mexiletine.

For SBRT planning, resting myocardial perfusion ammonia-13 positron emission tomography / computed tomography (CT), late gadolinium enhancement magnetic resonance imaging (MRI), and gated-cardiac CT angiogram were coregistered with the planning 4D-CT scan using fiducials like bony landmarks, cardiac implantable electronic device (CIED) leads/components, and cardiac silhouette in the radiotherapy planning software (Eclipse v15.6; Varian Medical System, Palo Alto, CA). Informed by the clinical VT electrocardiogram (ECG) morphology, the treatment target was contoured to include the severe perfusion defect that correlated with late gadolinium enhancement involving the distal LV anterolateral wall and apex on MRI. The cardiac CT angiogram was used to contour the gross target volume (GTV) to cover the full wall thickness. The 4D-CT scan was used to expand the GTV for each GTV image slice to obtain the internal target volume (ITV). Additionally, a 5 mm margin was added to the ITV to create the planning target volume (PTV). The GTV, ITV and PTV were 55.6 cc, 68.1 cc, and 146.7 cc, respectively. In addition to contouring of adjacent organs like lung and gastrointestinal tract, components of the WiSE CRT system, ie, the intercostal transmitter (which was in very close proximity to the treatment target) and the left lateral subcutaneous battery pack, were also contoured (Figure 2).

The dosimetrist and radiation physicist then created a treatment plan to deliver 25 Gy throughout the PTV while limiting the dose delivered to radiosensitive organs. The dose to the WiSE system was limited to $<$10 Gy. This plan was accomplished by using 20 arcs to deliver the 25 Gy to the target and avoid any beams directed through the WiSE system components (Figure 3).

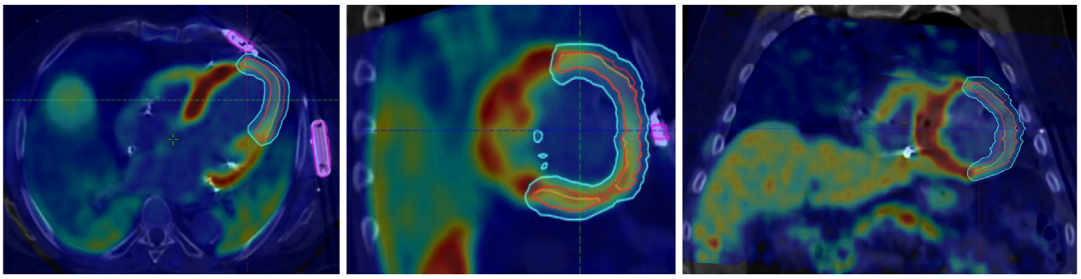

Figure 2 Axial, sagittal, and coronal views of computed tomography simulation scan overlay with positron emission tomography / computed tomography. Teal outlines indicate planning target volume; red, internal target volume; and yellow, gross target volume. Wireless Stimulation Endocardially for Cardiac Resynchronization Therapy indicated by pink outlines.

The patient underwent SBRT targeting the PTV with 25 Gy dose delivered in a single fraction. Cone beam CT, to align the cardiac structures with the radiation plan, was obtained after patient positioning on the treatment table with an abdominal binder to restrict respiratory motion and was repeated midway during SBRT treatment. The beam-on time for the treatment was 51 minutes. Three dosimeters were placed over the ICD generator, WiSE transmitter, and battery pack and the dose to these was measured 0.42 Gy, 7.5 Gy, and 5.3 Gy, respectively. The ICD and WiSE devices were interrogated after completion of SBRT and showed appropriate functioning.

He was discharged home on mexiletine 300 mg twice daily and amiodarone 200 mg twice daily. Mexiletine was completely weaned off by 3 months post SBRT and amiodarone weaned off by 7 months post SBRT. Anticoagulation was continued owing to history of atrial fibrillation. Over the 9-month post-SBRT follow-up, the patient has not had any clinical or device-logged recurrence of sustained VT (despite programming to detect VT $\geq$105 beats/min). An echocardiogram obtained 3 months post SBRT showed a mild improvement in LVEF to 30%. He successfully completed cardiac rehabilitation with clinical improvement in his functional status from NYHA class III to II. WiSE CRT function and battery status have remained stable.

Discussion

Cardiac SBRT is a novel noninvasive treatment for refractory VT. Catheter ablation remains the treatment of choice for management for VT in patients who have failed or do not tolerate antiarrhythmic drugs. However, the safety and efficacy of catheter ablation may be limited by various clinical and technical factors. Cardiac SBRT is an emerging modality that can be considered for patients with structural heart disease and recurrent monomorphic VT who have failed or have contraindications to catheter ablation. It involves delivering precise, high-dose gamma radiation in a single fraction to the myocardial VT substrate.

Small case series have shown cardiac SBRT to be an effective and safe procedure in patients with refractory monomorphic VT[1] as well as electrical storm.[2] One of these patients suffered a fatal stroke 3 weeks after SBRT though it is uncertain if this was a treatment related event.[1] As a result, the current practice is to anticoagulate patients for 3 months post cardiac SBRT. Limited long-term follow-up data for safety and efficacy of cardiac SBRT is currently available. A case series of SBRT in 10 patients with a median follow-up of 28 months showed a possible late cardiac radiation–related toxicity in the form of progressive mitral regurgitation.[3] The ENCORE-VT trial was a prospective phase I/II clinical trial that was conducted to assess safety and efficacy endpoints in 19 patients undergoing cardiac SBRT for treatment-refractory VT or premature ventricular contraction–induced cardiomyopathy. In patients undergoing SBRT for VT, there was 94% total VT episode reduction as well as a significant reduction in median number of ICD shocks and ATP. No acute toxicity or adverse effects with ICDs were observed. There were modest short-term adverse effects. There was a probable treatment-related serious adverse effect within 90 days after SBRT in the form of pericarditis that improved with medical management.[4] There were 2 late serious adverse events. One patient developed a pericardial effusion at 2.2 years and another patient developed a gastropericardial fistula at 2.4 years that was successfully treated with surgery.[5]

Conventional CRT for heart failure has many limitations in current practice. This is owing to procedural limitations of coronary sinus lead placement as well as nonresponders, resulting in a significant proportion of patients being unable to reap the benefits of CRT. The WiSE CRT has CE Mark approval in Europe but is an investigational device in the United States that performs leadless LV pacing without the need for prolonged oral anticoagulation. It consists of a receiver electrode implanted in the left ventricle and a transmitter implanted in the intercostal space that is connected to a subcutaneous battery.

A high success rate of WiSE CRT device implantation was reported in the prospective nonrandomized SELECT-LV (Safety and Performance of Electrodes implanted in the Left Ventricle) trial[6] as well as in a multicenter international registry,[7] with an acute procedural and device-related complication rate of 8.6% and 4.4%, respectively. It is currently being studied in the prospective, 2-stage (randomized followed-by single-arm) clinical trial SOLVE CRT to provide CRT in conjunction with a right ventricular pacing

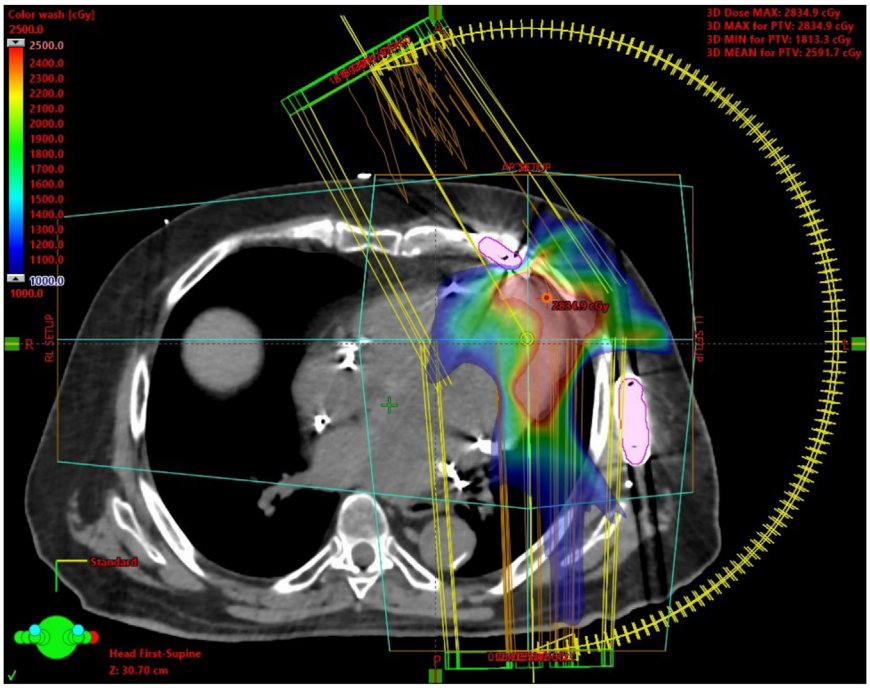

Figure 3 An axial computed tomography scan slice with stereotactic body radiotherapy treatment plan overlaid. Contours in pink mark the transmitter and battery of WiSE CRT system and are outside the 10 Gy dose region (blue). The ventricular tachycardia substrate in left ventricular apex received 25 Gy (red).

device in patients who are nonresponders to mainstream CRT, patients who have failed placement of or have a nonfunctional coronary sinus lead, and those who are high risk for device upgrade. In the nonrandomized roll-in phase of the SOLVE CRT study, 31 patients underwent WiSE CRT implantation. Six-month follow-up showed improvement in NYHA class in 14 patients and overall significant improvement in LVEF and LV volumes. Three device-related complications were reported, including inadequate LV pacing, embolization of an LV electrode, and a skin infection.[8]

Owing to limited experience with both SBRT and WiSE CRT systems, the safety and feasibility of SBRT in the presence of a WiSE CRT device has not been reported. We report a case of SBRT performed in a patient with WiSE CRT and bring to attention the importance of detailed planning prior to SBRT via a multidisciplinary team approach. This includes the cardiac electrophysiologist, radiation oncologist, and medical physicist. The structural VT substrate is identified using imaging modalities such as echocardiogram, cardiac MRI, cardiac CT, and radionuclide imaging, whereas information regarding the VT circuit is obtained from ECG and the electroanatomic mapping from prior invasive electrophysiology studies. The target volume is then delineated on the 4D planning CT after integration with other imaging modalities. The GTV is contoured based on input from the electrophysiologist, who analyzes the available information to define on the planning CT the region to be targeted. The radiation oncologist and the electrophysiologist then determine the penumbra of the treatment region to be added to the GTV to form the ITV in view of factors like unaccounted cardiac and respiratory motion and extension of arrhythmogenic substrate outside of the contoured GTV. Finally, an additional safety margin is added to the ITV to account for unrecognized misregistration, beam orientation, and alignment, and this is called the PTV.[1] The radiation oncologist contours critical structures (eg, the lungs, gastrointestinal tract, and spinal cord) to avoid radiation injury to these radiosensitive structures. In this case, the components of the WiSE system, including the battery pack and the intercostal transmitter, were also contoured and the radiotherapy plan was created to limit radiation dose $<$10 Gy to the WiSE system.

Delivery of radiotherapy in presence of CIED is associated with radiation-mediated CIED malfunction. Though these effects are uncommonly seen, radiation delivered in proximity to electrical sensing hardware and circuitry can create electromagnetic interference that can inhibit pacing or lead to inappropriate ICD therapy. The cumulative dose delivered to various components of a CIED may affect the integrity of the CIED system, though such effects are inconsistent and, fortunately, rare. Regardless, the Heart Rhythm Society recommends limiting total dose to CIED $\leq$5 Gy if possible. If the CIED is in the direct field of the radiotherapy target, the CIED may need to be revised and placed on the contralateral side. In addition to the aforementioned risks, ionizing radiation including high-frequency x-rays/gamma rays used in SBRT and particle beam therapy including proton beam or carbon ions can generate neutron scatter. This can stochastically interact with the silicon semiconductors in the CIED electronics, with potential for reversible or irreversible hard resets and lockout, making the device malfunctional or causing premature battery depletion. All these risks

are applicable to the WiSE CRT system and may be amplified during cardiac SBRT owing to proximity of the ultrasound transmitter and the receiver electrode to the myocardium. As illustrated by our case report, careful SBRT treatment planning, even when the target is in very close proximity to the WiSE CRT hardware, can limit the overall dose delivered to the CIED and minimize any device malfunctions. Regardless, with >5 Gy dose expected to be delivered to the CIED, careful intra-treatment monitoring with continuous ECG and pulse oximetry should be considered, especially in pacing-dependent patients.[9]

Cardiac SBRT may serve as a last resort for refractory VT in critically ill patients with advanced heart failure in whom electrical and mechanical device support is indispensable. A retrospective analysis of 14 patients who received cardiac SBRT included 3 patients with LV assist devices (LVADs), all 3 of whom had VT recurrence and ultimately underwent orthotropic heart transplantation.[10] Another center reported their experience with SBRT for incessant VT in 2 patients with LVADs. The treatment planning was complicated by artefacts from the LVAD cannula, and both patients continued to have VT post SBRT and eventually died from multiorgan failure.[11] Both reports did not observe any LVAD dysfunction during or post SBRT.

In conclusion, cardiac SBRT is a salvage option for refractory VT in patients with structural heart disease. SBRT can be delivered safely in presence of cardiac electrical and mechanical devices that are often integral to the management of advanced heart failure patients. This requires careful planning to limit the dose delivered to the device hardware. WiSE CRT is an exciting newer option for delivering effective CRT in heart failure patients. Though more data is needed, presence of WiSE CRT should not be a contraindication for potentially lifesaving cardiac SBRT therapy.

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