Stereotactic Ablative Radiotherapy for the Treatment of Refractory Cardiac Ventricular Arrhythmia

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Case Report
A 71-year-old man with coronary artery disease, coronary artery bypass grafting in 2000, baseline ejection fraction of 0.24, and implantation of a single chamber implanted cardioverter defibrillator (ICD) in 2009 for ventricular tachycardia (VT) presented with continuous episodes of nonsustained and sustained VT refractory to sotalol and mexiletine. Despite angioplasty and stent for coronary artery disease, VT continued for 2 years. Medical history included atrial fibrillation and oxygen-dependent chronic obstructive pulmonary disease. Baseline electrocardiogram (ECG) showed atrial fibrillation with a ventricular rate of 82 beats per minute with inferior Q waves and QRS duration of 90 ms. Twelve-lead ECG during VT showed a regular, wide-complex tachycardia at 160 beats per minute (CL 380–400 ms), with a right bundle branch block pattern, superior axis, precordial transition at V3–V4. His ICD log showed numerous VT episodes, with a single morphology seen on intracardiac ventricular electrogram, cycle length 380–411 ms. Episodes were nonsustained, pace-terminated, and shock-terminated. As catheter ablation was relatively medically contraindicated, he consented to a Food and Drug Administration and Institutional Review Board–approved compassionate-use protocol of stereotactic arrhythmia radioablation (STAR), noninvasive ablation of VT substrate by stereotactic ablative radiotherapy (SABR) techniques for tumors. STAR therapy was delivered in October, 2012.

STAR Planning and Delivery
Baseline echocardiogram showed a dilated left ventricle (LV), ejection fraction of 0.24, with basal inferior aneurysm, and apical and infero-posterior akinesis. Positron emission tomography–computed tomography showed extensive hypometabolic scar in the LV extending between the LV base and the apex, involving the inferior, inferoseptal, and inferolateral walls. A target for STAR was delineated using proprietary visualization and contouring software (CardioPlan™, CyberHeart™, Portola Valley, CA), outlining the target volume corresponding to what would have been the likely catheter ablation volume for this VT substrate based on imaging-defined inferior LV scar and 12-lead ECG QRS morphology during VT, implying a likely inferior LV VT circuit location (Figure 1A). The target volume was transferred to the radiation treatment planning software (MultiPlan 4.6.0, Accuray, Sunnyvale, CA) of the treatment system (CyberKnife®, Accuray, Sunnyvale, CA), with normal organs delineated, including lungs, esophagus, and stomach.

A temporary pacing wire (Oscor, Inc., Miami Lakes, FL) was fluoroscopically placed in the RV apex as an imaging fiducial marker that could be dynamically tracked to compensate for respiratory motion (Synchrony® Respiratory Tracking 9.6.0, Accuray, Sunnyvale, CA). The magnitude of the remaining cardiac motion was determined by fluoroscopy of the fiducial marker during transient breath holds, and the final target volume included an expansion to encompass this residual motion. The finalized target was then used for treatment planning.

A STAR treatment plan of 25 Gy in a single outpatient treatment over 90 minutes to the 75% isodose line was designed (Figure 1B and 1C), encompassing the infero-septal, inferior, and infero-lateral walls from base to apex. The maximum dose of 33 Gy was centered in this extensive scar region, within the central mid-myocardial layer. Normal lung, stomach, and esophagus dose constraints typical of thoracic tumor SABR treatments were easily achieved.
Clinical Response

He tolerated the procedure well, requiring no sedation, with no complications. Sotalol dose periprocedurally was 80 mg bid, mexiletine 150 mg tid. Follow-up ICD interrogations revealed a decrease in total VT episodes from an average of 562 episodes per month in the 2 months pre-STAR to an average of 52 episodes per month in months 2 to 9 post-STAR (Figure 2). At 3 months post-STAR, frequent nonsustained and pace-terminated VT occurred, associated with reduction of the sotalol dose to 40 mg bid and mexiletine dose to 150 mg bid. Intracardiac electrograms from the patient’s ICD during VT were similar to those from pretreatment VT; however, the cycle length of the VT slowed from 380–411 ms to 470 ms pre versus post STAR. Titration of mexiletine and sotalol dosing back to 150 mg tid and 80 mg bid, respectively, resulted in no further episodes of VT. Repeat positron emission tomography–computed tomography at 2.5 months post STAR demonstrated mild extension of the inferior scar, with a more complete perfusion defect within the inferior scar.

Prospective quality of life assessment by the RAND Short Form (SF)-36 demonstrated general stability after treatment, despite progressive decline in overall health, with multiple subsequent admissions for COPD exacerbation (Figure in the Data Supplement). Echocardiograms at 1, 3, and 6 months showed no significant changes from baseline.

Nine months after STAR, the patient was admitted with COPD exacerbation and recurrent VT, despite sedation and intubation; sotalol was discontinued and amiodarone was initiated at 400 mg daily, despite underlying pulmonary disease. He expired because of respiratory failure, congestive heart failure, with recurrent VT. His family declined autopsy.

Discussion

We report the first-in-human treatment of a cardiac arrhythmia using stereotactic arrhythmia radioablation. STAR targeted the VT substrate in the LV myocardium, with no definite acute or late complications. Seven months of reduction in VT on a stable antiarrhythmic regimen suggest a possible transient benefit of STAR. Repeat positron emission tomography–computed tomography and VT cycle length slowing demonstrated likely treatment effect within the targeted myocardial scar. Twelve-lead ECG and intracardiac ICD electrograms were consistent with likely recurrence within the inferior LV STAR target. The transient decrease in VT post STAR suggests initial ablative efficacy followed by healing of the arrhythmia substrate versus inadequate radiation dosing overall. Thus, we hypothesize that radiation dose escalation could improve response durability, as suggested by recent preclinical data.1

Catheter-based ablation is an effective therapy for VT, but long-term response durability and medical or anatomic constraints limit patients’ candidacy.2 SABR is highly focused radiation therapy that targets well-delineated tumors with high accuracy and precision using image guidance.3 Multiple beams with computer-optimized intensities create 3-dimensional dose sculpting, concentrating ablative doses to the target, with a rapid dose fall-off to minimize toxicity to surrounding tissues. Intra-cardiac malignancies have been effectively and safely treated with SABR.4 Preclinical studies demonstrated electrophysiological conduction blockade and histological fibrosis after SABR to the cardiac conduction pathway, providing proof of principle for treating arrhythmias.5 Unlike thermal ablation that causes immediate coagulative necrosis and subsequent scarring, ablative radiation leads to a complex cascade of acute and chronic tissue effects, including microvascular endothelial cell apoptosis, oxidative injury, inflammation, and fibrosis. This tissue injury mechanism may account for the observed time course of clinical response and subsequent recurrence in the subject.6 Moreover, unlike catheter ablation, STAR ablation can be directed at the entire transmurality of the target lesion.

A significant limitation of this article is that only a single treated patient was evaluated, limiting conclusions that can be drawn from the data; however, this first-in-man study demonstrates feasibility of STAR. Given the need for more treatment options for patients with VT who have either failed or have contraindications to catheter ablation, further investigation of STAR is warranted. We are exploring optimal patient selection, target delineation, and radiation dose selection. The role of STAR for ablation of other cardiac arrhythmias also remains to be elucidated.

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Figure 1. Stereotactic arrhythmia radioablation (STAR) treatment plan. A, Simulated cardiac ablation contours (dark blue); B and C, Final target volume (blue/yellow) treated with 25 Gy (Green isodose line) with higher dose (Red 29 Gy isodose line) centered within the mid-myocardial layer.

Figure 2. Episodes of ventricular tachycardia (VT) as recorded by implanted cardioverter defibrillator (ICD) interrogation, both ICD treated (red) and nontreated (blue), over time. The dotted line represents the 2-month moving average over this time period, with a transient decline post-treatment. VF indicates ventricular fibrillation.
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