Short-term and long-term effects of noninvasive cardiac radioablation for ventricular tachycardia: A single-center case series

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BACKGROUND Noninvasive cardiac radioablation is reported to be effective and safe for the treatment of ventricular tachycardia (VT).

OBJECTIVE This study aimed to analyze the acute and long-term effects of VT radioablation.

METHODS Patients with intractable VT or premature ventricular contraction (PVC)–induced cardiomyopathy were included in this study and treated using a single-fraction 25-Gy dose of cardiac radioablation. To quantitatively analyze the acute response after treatment, continuous electrocardiography monitoring was performed from 24 hours before to 48 hours after irradiation and at the 1-month follow-up. Long-term clinical safety and efficacy were assessed 1-year follow-up.

RESULTS From 2019 to 2020, 6 patients were treated with radioablation for ischemic VT (n = 3), nonischemic VT (n = 2), or PVC-induced cardiomyopathy (n = 1). In the short-term assessment, the total burden of ventricular beats decreased by 49% within 24 hours after radioablation and further decreased by 70% at 1 month. The VT component decreased earlier and more dramatically than the PVC component (decreased by 91% and 57% at 1 month, respectively). In the long-term assessment, 5 patients showed complete (n = 3) or partial (n = 2) remission of ventricular arrhythmias. One patient showed recurrence at 10 months, which was successfully suppressed with medical treatment. The posttreatment PVC coupling interval was prolonged (+38 ms at 1 month). Ischemic VT burden decreased more markedly than nonischemic VT burden after radioablation.

CONCLUSION In this small case series of 6 patients, without a comparison group, cardiac radioablation appeared to decrease the intractable VT burden. A therapeutic effect was apparent within 1–2 days after treatment but was variable by etiology of cardiomyopathy.

KEYWORDS Cardiac radioablation; Ventricular tachycardia; Early antiarrhythmic effect; Electrophysiologic change; Safety

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Introduction

Noninvasive cardiac radioablation, termed stereotactic body radiotherapy (SBRT) or stereotactic ablative radiation therapy in the radiation oncology field, is a promising alternative treatment option for intractable ventricular tachycardia (VT), which is the most common cause of sudden cardiac death. The treatment target of SBRT is the substrate of arrhythmias, which consists of varying degrees of diseased myocardial tissue observed in patients with ischemic or nonischemic cardiomyopathies.

Compared with the direct thermal injury caused by radiofrequency catheter ablation, the presumed mechanism of the antiarrhythmic effect of radioablation is fibrosis, which occurs several months after irradiation. Proof-of-principle studies on SBRT for pulmonary vein isolation have demonstrated that radiation-induced fibrosis effectively blocks

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KEY FINDINGS

- This is the first study that administered continuously electrocardiography monitoring before and after cardiac radioablation to investigate its short- and long-term treatment effect.
- Cardiac radioablation has an immediate therapeutic effect, lowering the number of ventricular beats within 1 month or even within 1–2 days. The decreased burden was mainly from the markedly decreased ventricular tachycardia burden, rather than from the premature ventricular contraction burden.
- Different treatment responses according to ventricular tachycardia etiology or changes in coupling interval after radiotherapy were observed, and these findings need to be validated in future larger studies.

conduction.[1,2] Recently, we reported the early pathologic changes that occurred after cardiac radioablation in a rat model, suggesting that the early antiarrhythmic effects of the treatment arise from cell-to-cell conduction disturbances and cellular membrane instability without direct necrotic damage to myofibril arrangements, which differs from the mechanism of radiation-induced fibrosis or conventional catheter ablation.[3]

Previous studies on cardiac radioablation included a 6- to 12-week "blanking period" and were focused on long-term effects rather than early changes.[4,5] However, when treating patients with incessant fatal arrhythmia, the immediate responses after cardiac radioablation are also of importance.[6,7] In this prospective case series, we focused on the early (within 1 month posttreatment) and long-term antiarrhythmic effects of cardiac radioablation.

Methods

Study design

The HeartSABR (arrhythmias treatment in Heart using Stereotactic ABlative Radiation therapy) study is a prospective case series conducted at a single center. Informed consent for administration of radiotherapy (RT) during the study[8] was obtained from all participating patients. This study was approved by the institutional review board of the participating institution (No. H-1903-015-1014) and conducted in accordance with the tenets of the Declaration of Helsinki.

Study patients

Eligible participants were patients ≥19 years of age who had shown more than 2 documented episodes of VT on electrocardiograms (ECGs) or had received implantable cardioverter-defibrillator (ICD) therapy (shock or antitachycardia pacing) owing to sustained VT within 6 months or cardiomyopathy (left ventricular ejection fraction [LVEF] <50%) related to monomorphic premature ventricular contractions (PVCs) (>15%) before enrollment into this study. Each participant received and did not respond to standard therapy for VT, including antiarrhythmic drugs (unable to adapt to antiarrhythmic medications or uncontrolled VT even after 2 months of adequate treatment) or catheter ablation (treatment failure after catheter ablation or contraindication for catheter ablation, such as LV thrombosis, severe lung disease, vascular abnormality, and heart malformation), before enrollment. Patients were deemed ineligible if they had a LVEF lower than 15%. Patients were also ineligible if their life expectancy was <1 year, owing to any underlying disease except VT.

Delineation of the target volume

A synthesis of imaging studies, 12-lead ECG, and electrophysiological mapping were used to localize the treatment target (arrhythmogenic substrate on the ventricular myocardium) for cardiac radioablation. Various imaging techniques, including chest computed tomography (CT), cardiac magnetic resonance imaging, and single-photon emission CT, were used to identify and define ventricular scars. The imaging techniques used for each patient were determined by the attending physician. For patients with a history of catheter ablation, 3-dimensional electroanatomical mapping (CARTO 3 electroanatomical mapping system; Biosense Webster, Diamond Bar, CA) was used as the primary guide for cardiac radioablation.

A 2-mm-slice respiratory-gated 4-dimensional CT (4D-CT) simulation was performed using intravenous contrast enhancement. Considering the respiration amplitude, the internal target volume for half of the patients was delineated using the maximum intensity projection of the 4D-CT, while the adjacent organs at risk, including the lung, stomach, esophagus, and spinal cord, were delineated using the average intensity projection. However, all phases of 4D-CT were reviewed to take artifacts or blurring due to diaphragmatic movements into account. For the other half of the patients, the internal target volume and organs at risk were delineated using deep inspiration breath-hold CT because the target was very close to the stomach. For these patients, the planning organs at risk volume of the stomach was defined as the stomach with a 5-mm margin around it; planning target volume (PTV) was defined to avoid the planning organs at risk volume. The Eclipse system (Varian Medical Systems, Palo Alto, CA) was used for treatment planning, and volumetric modulated arc therapy planning was performed with a 10-MV flattening filter-free beam as previously described.[9]

Treatment

Patients received a single-fraction 25-Gy dose of SBRT delivered to the arrhythmogenic substrate using the TrueBeam linear accelerator (Varian Medical Systems) as defined in previous clinical trials and reports.[4,10] Neither a fiducial marker nor the gating technique was used because respiratory-gated 4D-CT simulation was performed. After patient setup, a cone-beam CT image was obtained and

compared with the simulation CT for accurate alignment of the target volume.

Outcome assessments

To assess the early antiarrhythmic efficacy of cardiac radioablation, continuous ECG recording with 24-hour Holter monitoring or telemetry was performed for all patients before and after cardiac radioablation. The recording was performed continuously from 1 day before RT to 2 days after RT. For patients with sustained VT, the numbers of VT episodes and ICD therapies before and after treatment were compared. For patients with PVC-induced cardiomyopathy, the total PVC burden before and after treatment was compared. However, for patients with long-term sustained VT, the severity of VT is obscured when the number of VT episodes is counted. To avoid this, the total number of ventricular beats was analyzed instead. The VT or PVC electrocardiographic characteristics of all patients, including length of tachycardia cycle, morphology, and coupling interval, were measured on 12-lead ECG the day before cardiac radioablation, the day of cardiac radioablation, 1 week post-RT, and 1 month post-RT. Afterward, patients underwent clinical follow-up scheduled at 3 months, 6 months, 9 months, and 1 year, during which they were evaluated for control of ventricular arrhythmia (efficacy) and occurrence of serious clinical events (safety). To assess long-term efficacy, either Holter monitoring or ICD interrogation was performed at 6 months and 1 year post-RT. The safety outcome included any kind of acute and late radiation-induced adverse events, and toxicity was evaluated according to the Common Terminology Criteria for Adverse Events version 5.0.

Statistical analysis

Data are expressed as mean ± SD for continuous variables and as numbers and percentages for categorical variables. Categorical variables were compared using the chi-square test, whereas the Student *t* test was used for the comparison of continuous variables. All statistical analyses were performed using SPSS version 25.0 (IBM Corp, Armonk, NY). The number of patients included in this study was too small for statistical comparison of post-RT changes with pre-RT profiles.

Results

Patient characteristics

From September 2019 to December 2020, we treated 6 eligible patients for intractable VT or PVC-induced cardiomyopathy using noninvasive cardiac radioablation. Table 1 shows the demographic and clinical data of each patient. The mean age of the patients at the time of treatment was 72 ± 7.4 years of age, and 2 of the patients were women. The included patients were eligible for this study because they showed VT storm (patient 1), incessant VT (patient 2, 4) PVC-induced cardiomyopathy (patient 3), or underwent

Table 1 Baseline demographic clinical characteristics of the 6 patients

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age, y	72	67	73	85	72	63
Sex	Male	Female	Female	Male	Male	Male
Body mass index, kg/m^2	30.4	22.9	21.9	25.4	24.7	25.6
NYHA functional class (1 mo before RT)	III∼IV	III	III	III∼IV	III∼IV	III∼IV
Baseline left ventricular ejection fraction, %	24	57	36	26	27	38
Hypertension	Yes	No	No	Yes	Yes	No
Diabetes	Yes	Yes	No	No	No	No
Chronic kidney disease	Yes	No	No	No	No	No
AAD before RT	Carvedilol, amiodarone	Amiodarone	Bisoprolol, carvedilol, amiodarone	Bisoprolol, amiodarone	Bisoprolol, carvedilol, amiodarone	Carvedilol, amiodarone
AAD after RT	Carvedilol, amiodarone	Bisoprolol	Bisoprolol	Bisoprolol, amiodarone	Bisoprolol, amiodarone	Carvedilol, amiodarone
No. of previous catheter ablation	1	2	1	0	1	0
Interval between last catheter ablation and RT, d	5	3	381	—	7	-
No. of previous percutaneous coronary intervention	0	0	0	0	1	2
No. of previous open heart surgery	1	0	0	3	0	0
Type of cardiomyopathy	Nonischemic	Nonischemic	Nonischemic	Ischemic	Ischemic	Ischemic
Study eligibility criteria	VT storm	Incessant VT	PVC-related cardiomyopathy	Incessant VT	Repetitive ICD therapies	Repetitive ICD therapies

AAD = antiarrhythmic drug; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association; PVC = premature ventricular contraction; RT = radiotherapy; VT = ventricular tachycardia.

Table 2 Target volume definition and treatment details

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Target location	RV outflow tract	LV summit	LV summit	Thinned LV wall	LV scar	LV scar
Gross target volume, cm^3	10.3	3.0	3.0	9.6	78.6	16.8
PTV, cm^3	45.1	17.5	26.8	108.3	246.8	59.3
Respiratory motion control	None	None	None	DIBH	CPAP	DIBH
PTV coverage, %	90.0	95.0	95.0	95.0	95.0	95.0
Dmax, Gy	35.7	28.2	28.6	28.3	30.9	30.7
Stereotactic body radiotherapy planning	2-arc	2-arc	3-arc	3-arc	3-arc	3-arc
Stereotactic body radiotherapy beam-on time, min	4.6	4.0	2.6	15.3	3.3	17.5
Total treatment time, min	7.6	5.9	4.9	77.4	5.6	25.9

CPAP = continuous positive airway pressure; DIBH = deep inspiration breath-hold; Dmax = maximal dose within target volume; LV = left ventricular; PTV = planning target volume; RV = right ventricular.

repeated ICD therapies (patients 5 and 6). All the patients were taking amiodarone as the antiarrhythmic drug at the time of evaluation. All but 1 patient were treated with a beta-blocker. Two patients had contraindications for invasive catheter ablation—1 (patient 4) had mechanical prosthetic mitral and aortic valves and the other (patient 5), who showed no response to previous catheter ablation, had LV thrombus. All 6 patients had New York Heart Association functional class III or IV heart failure symptoms. The mean LVEF was 34 ± 12.3%.

Treatment characteristics

The definition of the target volume and treatment details are presented in Table 2. The target was located in the right ventricular outflow tract (patient 1), LV summit (patient 2, 3), thinned LV wall (patient 4), or LV scar (patient 5, 6). The mean gross target volume was 20.2 ± 29 cm^3 and the mean PTV was 83.9 ± 85.9 cm^3. PTV coverage was 95% in 5 of the patients (ie, 95% of PTV received prescribed dose), and the maximum point dose was 30.4 ± 2.8 Gy. The mean beam-on time was 7.8 ± 6.6 minutes, and the mean treatment time, including patient setup, was 21.2 ± 28.6 minutes. The treatment time was exceptionally long for patients 4 and 6 because their respiratory motions were controlled using deep inspiration breath-hold because they could not hold their breaths during the entire treatment, and the beam delivery had to be stopped intermittently.

Early treatment response to cardiac radioablation

The baseline total number of ventricular beats (both VT and PVC) varied among the 6 patients, ranging from 1352 to 143,908 beats/d (mean 35,234 beats/d). The total number of ventricular beats per day decreased dramatically by 49% within 24 hours after cardiac radioablation. By 1 month after cardiac radioablation, the total number of ventricular beats decreased to 30% of the pre-RT value (Figure 1A). At the 1-month follow-up, the total number of ventricular beats for the 5 patients with VT decreased to 16% of their baseline values. Although the patient with PVC-induced cardiomyopathy (patient 3) showed a 28% decrease in the total number of ventricular beats at 48 hours, the number increased to 101% at 1 month post-RT.

The decreased burden was mainly from the markedly decreased VT burden, rather than from the PVC burden (Figures 1B and 1C). While the PVC burden did not decrease immediately after cardiac radioablation and later decreased to 42% of the baseline value at 1 month post-RT, the VT burden decreased immediately after RT to 20% of the baseline value and further decreased to 9% of the baseline value at 1 month after cardiac radioablation. Although the longest pre-RT VT run varied among the patients with VT (mean 1269 sustained beats; range 57–6000 sustained beats), the number of ventricular beats of the longest VT run decreased to 15% of its baseline value (Figure 1D). At the 1-month follow-up, all 5 patients with VT experienced no episode of sustained VT (sustained VT for over 30 seconds). The mean value of VT rate of the patients with VT also decreased to 61% of its baseline value at the 1-month follow-up (Figure 2A). Figure 2B shows a representative example of discontinuation of VT after cardiac radioablation. In terms of VT etiology, the total number of ventricular beats decreased more dramatically in patients with ischemic cardiomyopathy than in patients with nonischemic cardiomyopathy (Supplementary Figure 1).

Changes in coupling interval as a predictive marker for early treatment efficacy

The morphologic characteristics of changes in VT (or PVC) were observed. The coupling interval (ie, the interval from the QRS onset of the preceding sinus to the onset of the premature ventricular beat) was prolonged after cardiac radioablation. The coupling interval increased to 25 ms immediately after RT and to 25 ms the day after RT and further increased to 48 ms at the 1-month follow-up (Figures 3A and 3B). Figure 3C shows a representative image of the temporal changes in the coupling interval.

We divided the patients into 2 groups according to their treatment response at the 1-month follow-up. Four patients whose total number of ventricular beats decreased to <5% of the baseline value were included in the good responder group, whereas the other 2 patients were included in a poor

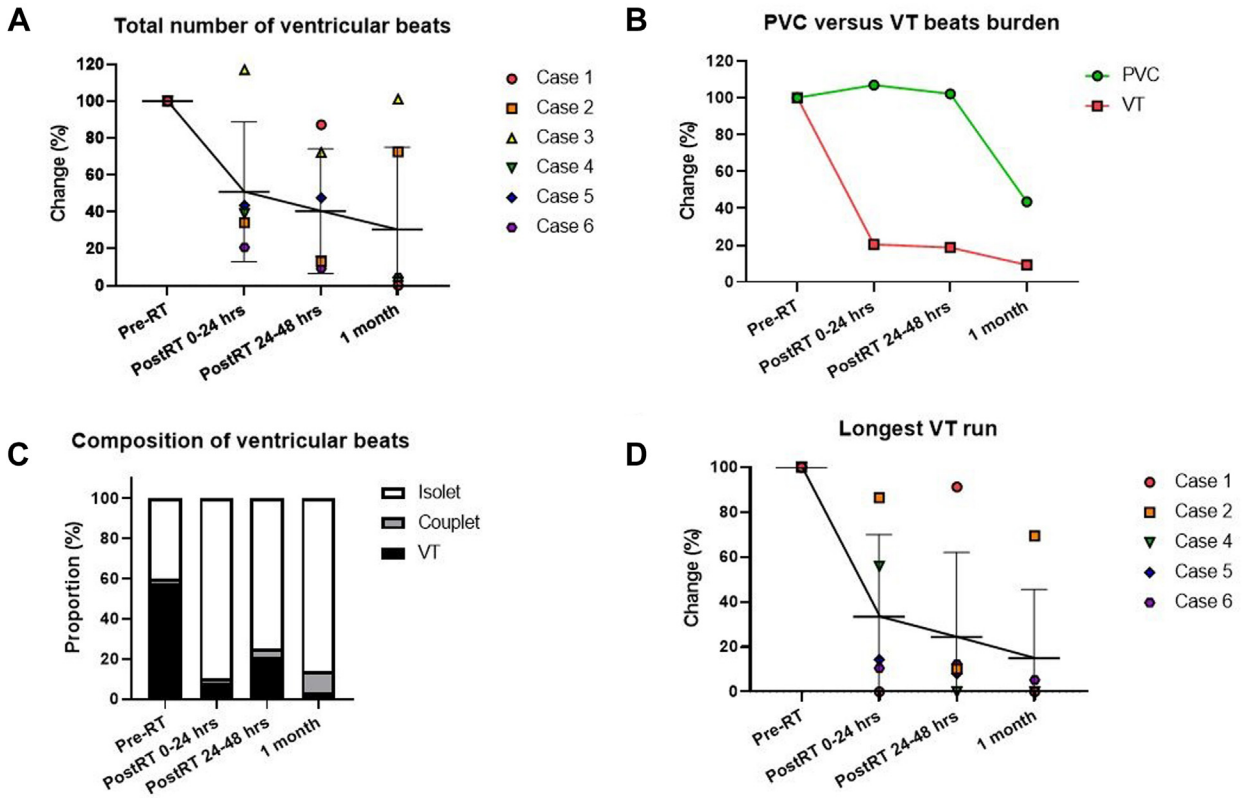

Figure 1 The relative changes in the total number of ventricular beats **(A)** and premature ventricular contraction (PVC) and ventricular tachycardia (VT) burden (**B**) from the pre-radiotherapy (RT) day. **C:** The changes in composition of ventricular beats after cardiac radioablation. **D:** The relative change in duration of the longest VT run in all patients from the pre-RT day. Data are presented as mean ± SD.

responder group. Excluding 1 patient (patient 4) whose coupling interval data were not available because of no ventricular beat, the good responder group showed an 84% increase in coupling interval, whereas the poor responder group showed an 8% decrease from baseline (Figure 3D).

Long-term evaluation of treatment outcomes

At a median follow-up time point of 12.3 months, no patient had undergone any invasive salvage treatment, such as radiofrequency catheter ablation or cardiac surgery. Three patients showed complete remission of VT on cardiac implantable device monitoring. Two patients showed partial remission of ventricular arrhythmias that were controllable with medication. One patient showed VT recurrence at 10 months, which was successfully suppressed using medical treatment. Before cardiac radioablation, 9 unplanned outpatient or emergency room visits were recorded in 115.5 patient-months. In contrast, the number of unplanned visits decreased to 2 visits in 82.1 patient-months after cardiac radioablation.

In addition, there was no change of the antiarrhythmic drugs in 4 out of 6 patients after cardiac radioablation.

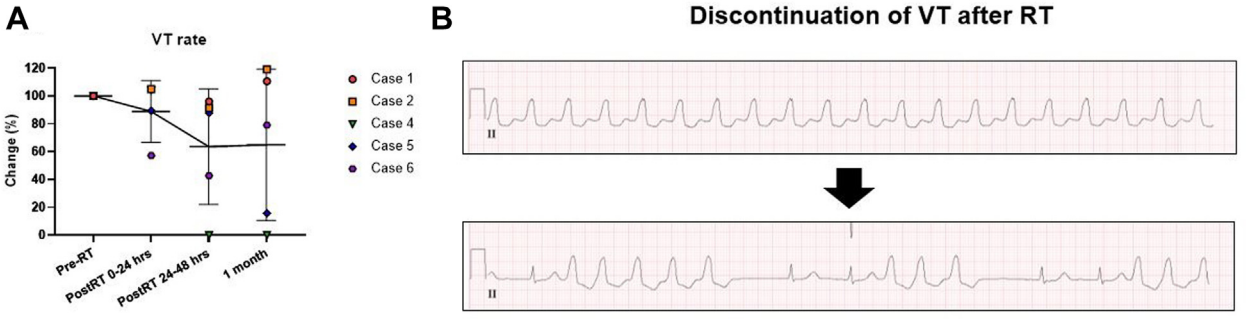

Figure 2 **A:** The relative change in the rate of ventricular tachycardia (VT) from the pre-radiotherapy (RT) day. **B:** Representative example of discontinuation of VT after cardiac radioablation. Data are presented as mean ± SD.

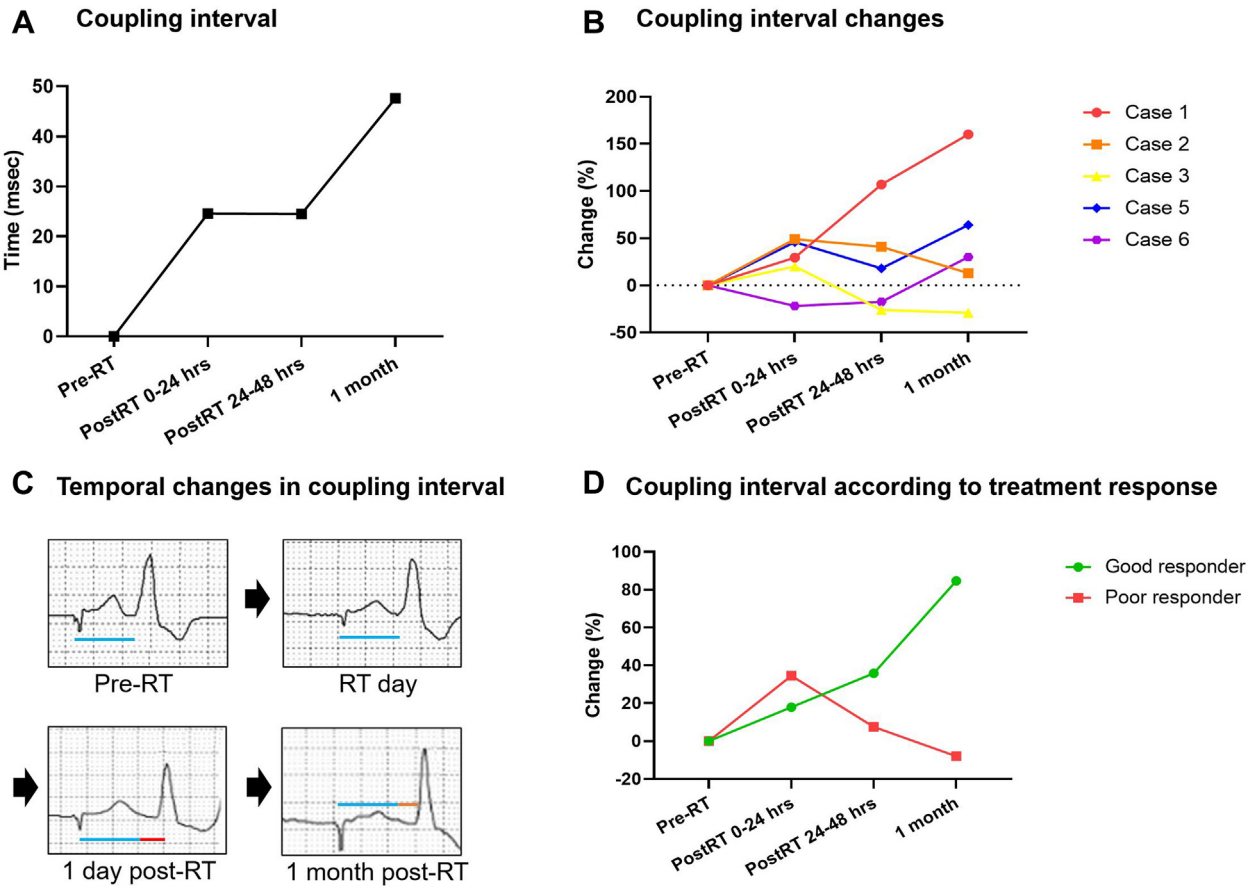

Figure 3 **A:** The absolute change in coupling interval in all patients from the pre-radiotherapy (RT) day. **B:** The relative change in coupling interval in each patient from the pre-RT day. **C:** Representative image of temporal changes in coupling interval. (**D**) The relative change in coupling intervals in good responders and poor responders from the pre-RT day.

Amiodarone was administered to all of the patients; 2 of them were able to quit amiodarone immediately after cardiac radioablation, and 1 patient (patient 6) stopped the use of amiodarone a year after the procedure.

Safety

No acute adverse event exceeding grade 2 was recorded at the 1-month follow-up after cardiac radioablation. However, 1 case of each grade 1 fatigue, abdominal discomfort, and nausea were recorded. One patient experienced a grade 2 heart failure aggravation, which was managed well using medical treatment. At 1-year follow-up, 1 case of grade 2 abdominal discomfort and 1 case of grade 3 heart failure aggravation, which required insertion of a LV assist device, were recorded. One patient (patient 5) died of pneumonia, which was not likely treatment-related, at 7.7 months after cardiac radioablation. No patient presented with a substantial reduction in LVEF compared with baseline (Figure 4). Before cardiac radioablation, 3 admissions due to heart failure were recorded in 115.5 patient-months. Similarly, 3 admissions due to heart failure were recorded in 82.1 patient-months after cardiac radioablation.

Discussion

In this case series, we analyzed the short-and long-term effects of cardiac radioablation for VT. To our knowledge, this is the first report of the early treatment efficacy of cardiac radioablation administered with continuous ECG monitoring before and after treatment. Within the first month after cardiac radioablation, the longest sustained VT was markedly

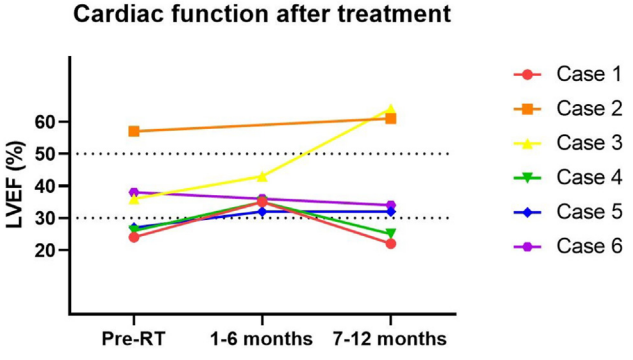

Figure 4 The changes in left ventricular ejection fraction (LVEF) during follow-up after cardiac radioablation. RT = radiotherapy.

shortened, leading to a decrease in the total burden of ventricular beats. The decreased burden was mainly from the markedly decreased VT burden, rather than from the PVC burden. The treatment effect was maintained without significant adverse events at 1-year post-RT. This study is also the first to show the changes in coupling interval and its prognostic potential for early treatment response after cardiac radioablation for VT. We speculate that the therapeutic effect of cardiac radioablation could be expected within 1 month or even within 1–2 days after treatment.

Radiation is traditionally used for the treatment of cancer. Ionizing radiation not only induces apoptosis of cancer cells through DNA damage, but also causes fibrosis in normal cells through connective tissue remodeling.[11] In previous preclinical studies, cardiac radioablation was studied under the concept that the late radiobiological effects of radiation (fibrosis) would contribute to the antiarrhythmic effect of the treatment.[12,13] Therefore, the antiarrhythmic effect of the treatment was predicted to occur a few months later because radiation-induced fibrosis usually appears several months after RT. In addition, the concept of a blanking period after cardiac radioablation was adopted in these studies. A 6- to 12-week blanking period was set after cardiac radioablation in these studies, with the focus on the treatment response after the blanking period, rather than on the immediate treatment responses.[4,5,10]

Some case reports and studies have shown the early effects of radioablation. In these previous reports, the time to decrease in VT burden varied from 6 days to 6 weeks after cardiac radioablation.[6,10,14–16] The putative pathological and electrophysiological findings of some preclinical studies have been suggested as the mechanisms underlying the therapeutic effects of RT before the onset of fibrosis.[3,17–20] Several preclinical studies have shown that irradiation induces alteration in the expression of connexin 43 and changes in gap junction distribution, which explains the change in intercellular conductivity.[17,18] Recent study data provides probable evidence of radiation-induced reprogramming of cardiac conduction, including the increased function of the cardiac sodium channel and improved conduction, which could be a potential mechanism of the antiarrhythmic effect of cardiac radioablation.[20]

One of the major findings of the present study is the prominent and immediate reduction of the VT burden, rather than the PVC burden after radiotherapy. In addition, we observed that the response to cardiac radioablation was better in patients with ischemic VT than in those with nonischemic VT. The response to electrophysiologic changes caused by irradiation may vary depending on the characteristics of the ventricular tissue (ie, VT substrate). We hypothesized that RT affects the refractory period or electrophysiologic characteristics of the VT substrate, leading to instability of the subsequent reentry circuit, which interrupts the sustainability of VT. Our observations in the present study support this hypothesis. However, conflicting results of previous studies showed a notable response in some patients with nonischemic cardiomyopathy,[5,10] and the inclusion of small number of heterogeneous patients in the present study reduced the power of the conclusion. Therefore, further studies that include a large number of patients are warranted to verify our findings.

The present study is the first to show the changes in the coupling interval of PVCs after irradiation. A short coupling interval is known to be associated with malignant ventricular arrhythmias,[21] and antiarrhythmic drugs, such as amiodarone, increase the coupling interval by prolonging the refractory period of the ventricular tissue.[22] In addition, VT with a long coupling interval is associated with a low incidence of sustained VT events.[23] In the present study, the good responders to cardiac radioablation showed prolonged coupling intervals at 1 month after cardiac radioablation compared with the poor responders. Although this finding needs to be validated, these changes in coupling intervals may represent early radiation-induced alteration during the refractory period. Recent study with human cardiomyocyte showed increased conduction velocity after irradiation, which gives clue for the interpretation of our findings.[24] In contrast, a conflicting result that cardiac radioablation did not affect the conduction velocity was also reported.[3] However, we suppose that the change of coupling interval is attributable to the interaction between diseased tissue and normal adjacent cells that is yet to be identified.

No severe adverse events were reported in this study. However, 1 patient (patient 5) died of pneumonia at 7 months post-RT. The death was considered a non–treatment-related adverse event because the patient did not develop RT pneumonitis. Two patients (patients 4 and 6) were hospitalized for heart failure management at 8 and 5 months after cardiac radioablation, respectively; however, there were no recurrent VT episodes in the ICD logs of both patients. One patient (patient 6) presented with chronic progressive heart failure with reduced LVEF and is preparing for insertion of a LV assist device. It is meaningful that the patient had a LV assist device–free period more than approximately 1 year after cardiac radioablation.

This study has a limitation. This was a single-center prospective case series with a small sample size. The number of participants was inevitably small because the cardiac radioablation was only targeted at patients who did not respond to medical treatment and were unable to or did not respond to catheter ablation. Although we performed further analysis regarding the etiology of VT, the reliability of the interpretation would be limited owing to the small sample size.

Conclusion

In patients with intractable VT, treatment using 25 Gy of noninvasive cardiac radioablation resulted in an immediate decrease in the number of ventricular beats in part of the patients before tissue fibrosis is expected to occur. The decrease in VT burden through the shortening of VT began within 24 hours after the procedure and continued to decrease until 1 year after the treatment. Different treatment responses

according to VT etiology or changes in coupling interval were observed. However, these findings need to be validated in future larger studies.

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Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: Informed consent for administration of radiotherapy during the study (HeartSABR, KCT0004302) was obtained from all participating patients.

Ethics Statement: This study was approved by the institutional review board of the participating institution (IRB No. H-1903-015-1014) and conducted in accordance with the tenets of the Declaration of Helsinki.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2022.11.006

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