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INNOVATIONS IN CLINICAL ELECTROPHYSIOLOGY

Radiation-Induced Changes in Ventricular Myocardium After Stereotactic Body Radiotherapy for Recurrent Ventricular Tachycardia

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ABSTRACT

Stereotactic body radiotherapy (SBRT) has been suggested as a promising therapeutic alternative in cases of failed catheter ablation for recurrent ventricular tachycardias (VTs) in patients with structural heart disease. This case series is the first postmortem immunohistochemical analysis of morphologic changes in the myocardium early and late after SBRT. The present findings are in line with experimental observations on apoptosis followed by fibrosis. This may explain why the effect of SBRT on VT is not predominantly immediate. Together with observation of early recurrences after SBRT for VT, these data suggest that this strategy may have rather delayed antiarrhythmic effects.
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Recently, stereotactic body radiotherapy (SBRT) has been suggested as a promising therapeutic alternative in cases of failed catheter ablation for recurrent ventricular tachycardias (VTs) in patients with structural heart disease (1). However, the exact mechanism of action of SBRT on the human myocardial substrate is not fully understood. Tissue changes were described either a few weeks after SBRT and/or much later (2,3). To our best knowledge, there are no previous data on morphologic changes within directly irradiated human hearts at 3, 6, and 9 months after SBRT.

CASE 1

A 52-year-old man with nonischemic cardiomyopathy and atrioventricular block underwent implantation of a cardiac resynchronization therapy defibrillator in 2016. In December 2018, he underwent catheter ablation for an electric storm. A total of 7 configurations of VT (rate 153-210 beats/min) were inducible. Epicardial ablation was performed across the scar area on the lateral wall. For persistent inducibility of 2 VTs from the upper and lower parts of the scar, mapping of the aorta and the left main orifice was performed for future coregistration for SBRT, as

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ABBREVIATIONS AND ACRONYMS

SBRT = stereotactic body radiotherapy

VT = ventricular tachycardia

described recently by our group (4). The patient presented with early recurrences of VT (at 160 beats/min) and was referred for SBRT. A single dose of 25 Gy was delivered to the left ventricular (LV) lateral wall substrate (planned target volume [PTV] 52 cm^3) using the strategy described earlier (4). Early after SBRT, the patient had a cluster of VT recurrences, interrupted by antitachycardia pacing. He had no signs of radiation pneumonitis. Two months later, the patient was readmitted for a recurrent electric storm, and echocardiography showed a further decrease of LV ejection fraction to 20% and severe right ventricular dysfunction. He was intubated and deeply sedated. Additional epicardial ablation was performed on the LV free wall and in the right ventricular outflow tract and free wall region (**Figure 1**). Subsequently, he developed sepsis caused by respiratory infection and was treated with antibiotics. For further recurrences of VT, the patient underwent implantation of biventricular support (HeartMate 3 [Abbott] and CentriMag [Levitronics]). The postoperative course was complicated by renal failure that required continuous renal replacement therapy. Despite combined antibiotic therapy, the patient became comatose and developed ischemic lesions in the colon and hepatic failure. He died 13 weeks after SBRT of multiorgan failure.

Following gross evaluation of the heart, a routine autopsy was performed with subsequent fixation in 10% formalin. Tissue samples were processed to paraffin blocks. Histologic sections were evaluated using standard hematoxylin and eosin, and sirius red with resorcin-fuchsin staining. Immunohistochemistry was performed as described previously (5). Routine histologic evaluation revealed myocytolysis corresponding to a previously irradiated region with a sharp transition to a viable myocardium (**Figure 2A**). Detection of caspase-3 as a marker of apoptosis revealed intracellular immunoreactivity in the cytoplasm of macrophages in the irradiated region (**Figure 2B** and **Central Illustration**).

CASE 2

A 57-year-old man was resuscitated for out-of-hospital cardiac arrest in 2017 and underwent implantation of a single-chamber implantable cardioverter-defibrillator (ICD). Detailed examination revealed coronary artery disease and severe LV dysfunction (LV ejection fraction 25%) with inferolateral aneurysm. Three months later, he underwent endocardial catheter ablation for an electric storm. In January 2018, endo- and epicardial ablation of a substrate on the inferolateral wall was performed for recurrences of VT. The patient was admitted 11 months later for recurrences of VT. SBRT was indicated and completed in December 2018. Inferolateral postinfarction scar was targeted (25 Gy delivered to the PTV of 62.1 cm^3). He had few recurrences of VT early afterward. After 6 months of freedom from any arrhythmia, the patient died suddenly out of hospital in July 2019.

The coroner determined the cause of death to be acute anterior myocardial infarction. ICD memory at the time of death showed episodes of refractory ventricular fibrillation that was terminated only transiently by a shock. Routine histologic staining of the radiated region revealed fibrosis with a sharp transition to viable myocardium. The fibrotic irradiated region contained densely packed fibers, including a relatively high elastic component (**Figure 2C**). Only a small number of cells immunoreactive for caspase-3 were found.

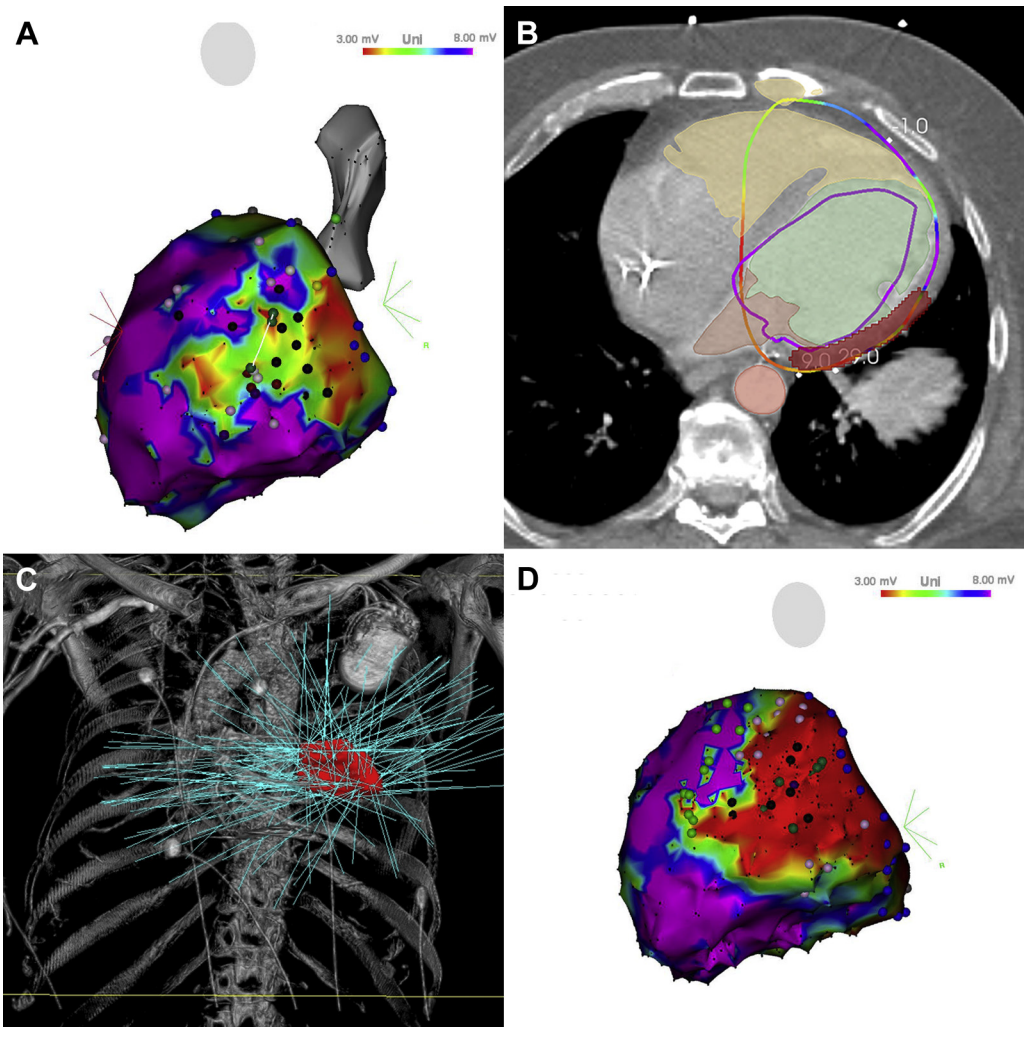
HIGHLIGHTS

- SBRT for recurrent VT is a promising strategy after failed catheter ablation.
- Our data suggest that SBRT results in apoptosis with subsequent fibrosis.
- These observations suggest that SBRT may have rather delayed antiarrhythmic effects.

CASE 3

A 67-year-old patient with a history of inferior myocardial infarction and coronary artery bypass surgery in 2000 underwent implantation of an ICD and later was referred for catheter ablation because of recurrences of VT. Three different configurations of VT were induced, originating from the inferior scar. Despite noninducibility at the end, the patient had recurrences of 2 faster VTs. In June 2018, SBRT was performed on the basis of positron emission tomographic/computed tomographic identification of the scar, and the PTV encompassed the entire scar volume (70 cm^3). The patient presented with early esophagitis (18 days afterward), but all symptoms resolved on antiulcer therapy. Two early recurrences of VT were noted (25 and 55 days afterward). Six months after SBRT, the patient was admitted for dysphagia, and a large ulcer in the terminal part of the esophagus was diagnosed. Despite percutaneous endoscopic gastrostomy insertion, the patient was readmitted 3 months later for progression of

FIGURE 1 **The Effect of SBRT on the Arrhythmogenic Substrate in Case 1**



(A) Unipolar epicardial voltage map before stereotactic body radiotherapy (SBRT) with patchy scarring on the lateral left ventricular wall. **(B)** Integration of the electroanatomical map with planning computed tomography with a highlighted target for SBRT **(red)**. **(C)** The target for SBRT with prescribed radiotherapy doses. **(D)** Unipolar epicardial voltage map obtained 10 weeks after SBRT and 3 weeks before autopsy. There is an apparent new homogenous area of low unipolar voltage, which corresponds to the histologic finding of myocytolysis (Figure 2A).

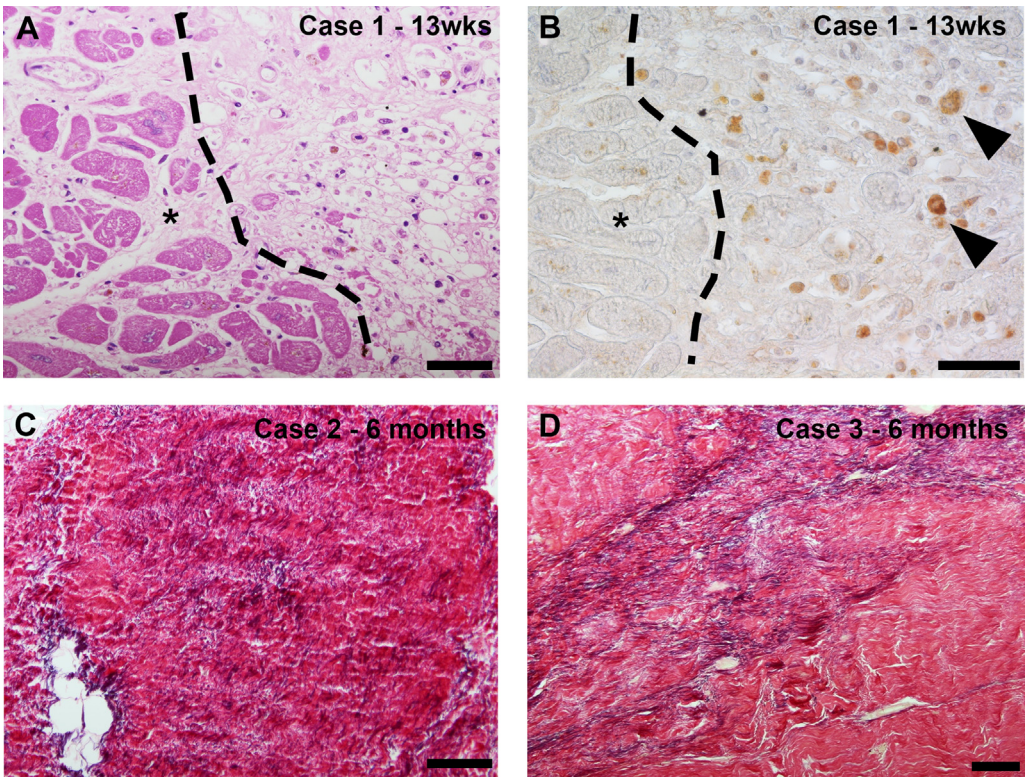
symptoms. Corrective surgery was contraindicated for high risk. A few days later, severe bleeding occurred and the patient died because of asystole after transient stabilization.

Macroscopically, a deep defect was seen in the distal part of the esophagus (2 × 3 cm), opening into a pericardial space with adhesions around and a necrotic rim. Visceral pericardium formed the ground of the defect and was colored gray to black with a rough surface. Histologic staining of the radiated myocardium revealed fibrosis with a sharp transition to viable myocardium. Marked elastosis was present in these regions (Figure 2D). Practically no cells immunoreactive for caspase-3 were observed.

DISCUSSION

The presented 3 clinical cases provide several important lessons for the clinical application of SBRT in VT management. First, using our strategy of coregistration of electroanatomical maps with computed tomography, we were able to reconstruct postmortem with high accuracy the boundary of the irradiated region. This was confirmed by histologic examination that showed sharp delineation from the surrounding

FIGURE 2 Histological Changes in Ventricular Myocardium after SBRT

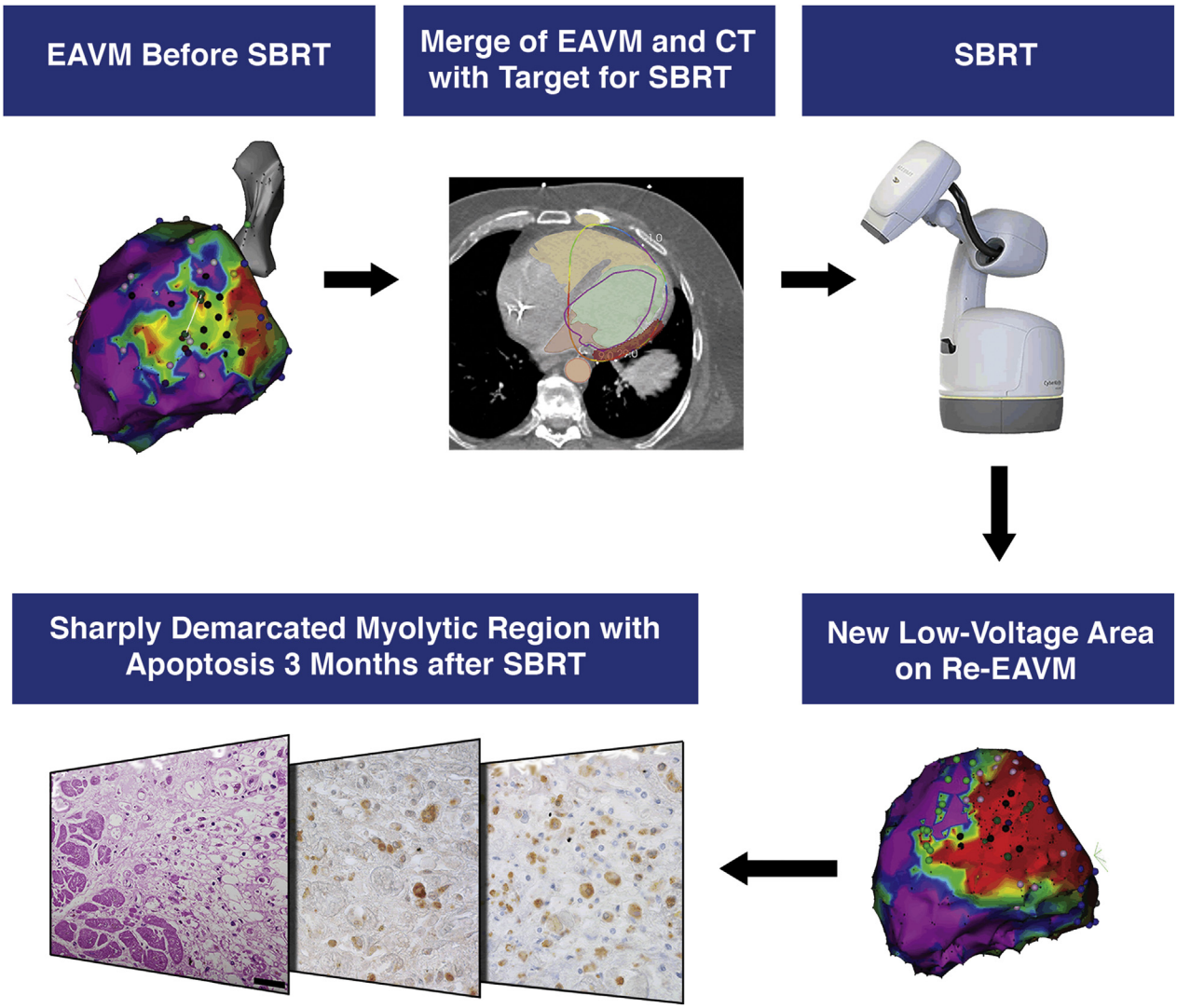


Case 1 (13 weeks after stereotactic body radiotherapy [SBRT]): routine histologic evaluation revealed myocytolysis corresponding to a previously irradiated region with a sharp transition to viable myocardium **(A)**. Detection of active caspase-3 as a marker of apoptosis revealed intracellular immunoreactivity in the cytoplasm of rounded cells that morphologically corresponded to macrophages **(B)**. Case 2 (6 months after SBRT): histologic staining of the irradiated area revealed fibrotic region containing densely packed fibers, including a relatively high elastic component **(C)**. Case 3 (9 months after SBRT): histologic staining of the irradiated region revealed myocardial scarring with marked elastosis **(D)**.

myocardium. Second, tissue changes described in our 3 patients correspond to the experimental findings of early and delayed effects of SBRT. Experimental irradiation of rat myocardium revealed apoptosis within the first 5 months, leading to the subsequent replacement of myocardial cells by fibrous tissue (6). Another study in irradiated pig hearts revealed at 3 months inflammatory changes with cleaved caspase-3 (a marker of apoptosis) and fibrosis at 6 months (7). This experimental evidence is in line with our observations. At 3 months, most of the apoptotic cardiomyocytes were phagocytosed by macrophages that contained caspase-3. This indicates that myocardial cell death caused by apoptosis is an early phenomenon. At 6 months, fibrosis was documented with marked elastosis. Third, complex arrhythmogenic substrates that are difficult to modify by catheter ablation may not be suitable to SBRT either. The first case documented the extension of the substrate to the right ventricle over time and thus the limited possibility to irradiate several regions of the heart at once.

These 3 cases may also raise concern about the safety of SBRT for recurrent VT. The death of the third patient was related to SBRT. In contrast, the first patient died of complications associated with recurrences of VTs. The second patient died suddenly because of myocardial infarction recurrence. This was less likely related to SBRT, as the irradiated region was on the distant inferolateral wall. At this stage of knowledge, it is difficult to make any conclusions about the late toxicity of SBRT and possible prevention. In the patient with esophagopericardial fistula, the esophageal dose limits were not exceeded in volume, and probable contribution of altered vascular supply in this region after the use of the gastroepiploic artery for coronary revascularization might have played a role. This case may reemphasize the importance of accuracy in the exact delineation of the

CENTRAL ILLUSTRATION **The Process of Data Collection in Case 1**



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CT = computed tomography; EAVM = electroanatomical voltage mapping; SBRT = stereotactic body radiotherapy.

critical part of the myocardial substrate and the use of the smallest PTV.

Our histologic observations should be seen in the context of both experimental and clinical data on predominantly delayed effects of SBRT in the treatment of VTs. Experimental studies documented clinical effects after several weeks (7). Similarly, clinical experience shows rather delayed effect on VT occurrence. In an earlier case report, we observed the disappearance of VT episodes within 6 months after SBRT in a patient with cardiac myxoma (8). In our more recent case of repeated radiotherapy, the therapeutic effect was noted only after 3 months (4). Therefore, signs of apoptosis in the irradiated tissue, especially early after SBRT with subsequent fibrosis, suggest that the effect of SBRT is not predominantly acute. However, some anecdotal clinical cases demonstrated acute termination of an electric storm (9), and 1 experimental study suggested that early antiarrhythmic effects may be caused by cell-to-cell conduction disturbances and cellular membrane instability (10).

It is also important to mention that our observations are related to a specific radiotherapy platform,

CyberKnife, which allows better compensation for respiratory movements and smaller PTV. There is no information on potential differences in the resulting histologic changes in the tissue between different platforms.

In all cases (whether ischemic or nonischemic cardiomyopathy), early VT recurrences were observed after SBRT. This observation is in line with our previous study (4). Delayed development of fibrosis may be critical for the maximum effect of SBRT on myocardial substrate. However, our data do not exclude acute effects observed by some research groups. Both the immediate and long-term efficacy and safety of SBRT must be determined in randomized trials or registries.

In conclusion, our findings suggest that SBRT for VT induces initial apoptosis of cardiomyocytes in the irradiated region (during the first 3 months), followed by the development of dense fibrotic scar at 6 to 9 months.

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