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STEREOTACTIC RADIOABLATION IN CLINICAL PRACTICE FOR THE TREATMENT OF A PATIENT WITH VENTRICULAR TACHYCARDIA: CASE REPORT

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The aim of the study is the demonstration of the 1st clinical experience of stereotactic arrhythmia radioablation (STAR) of the patient with antiarrhythmic drug (AAD) refractory ventricular tachycardia (VT) in Russia. The results of STAR of 57 years old patient with AAD and multiple radiofrequency ablation refractory VT are described. This clinical study demonstrates efficacy and safety of STAR of VT.

Key words: ventricular tachycardia; radiation therapy; electroanatomical mapping; stereotactic arrhythmia radiosurgery

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Ventricular arrhythmias, including ventricular tachycardia (VT), are the leading causes of sudden cardiac death (SCD) globally [1]. N. Srinivasan et al. (2019) have reported that over 4.25 million people die annually from SCD worldwide [2]. Life-threatening VT usually develops in patients with prior myocardial infarction (MI) and those who are present with reduced left ventricular ejection fraction (LVEF). The incidence of VT ranges from 3 to 5%, but it is constantly increasing as a result of improved post-infarction survival and the possibility of VT appearing years after the initial MI combined with the progressive aging of the global population [3,4].

Recent clinical guidelines on the management of VT and prevention of SCD recommend the use of antiarrhythmic drugs, implantation of a cardioverter-defibrillator (ICD) for primary and secondary prevention of SCD, endocardial and epicardial catheter ablation, and alcohol ablation [4, 5]. Complex anatomy, structural heart disease, subepi- and subendocardial substrate location limit the success of radiofrequency ablation (RFA). The recurrence rate of VT after RFA in patients with

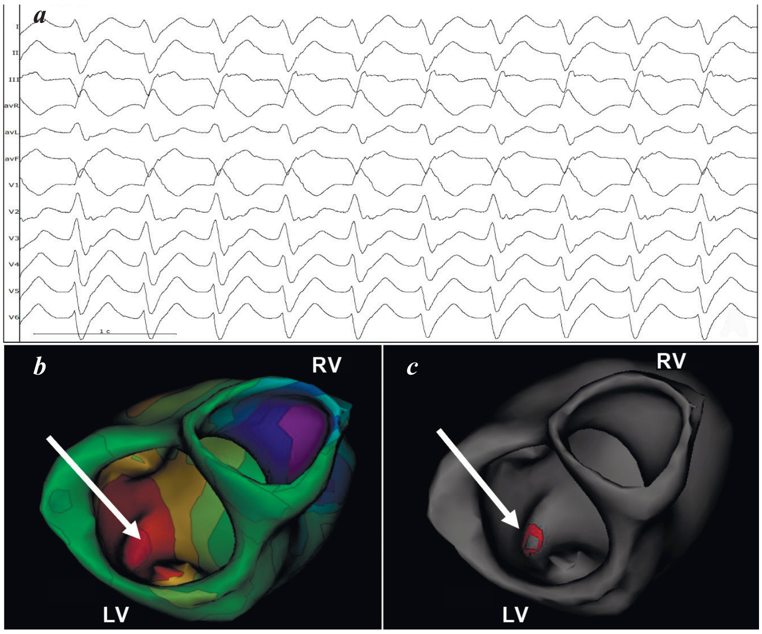

Fig. 1. Ventricular tachycardia mapping. a - Electrocardiogram of left ventricular tachycardia with a ventricular rate of 140 bpm. b, c - Non-invasive mapping of tachycardia. b - activation map, c - excitation propagation map. Note: the arrow shows the red zone - the area of early activation from the endocardial surface of the left ventricle. LV - left ventricle, RV - right ventricle.

structural pathology ranges from 12 to 17% within one year [6], despite a low rate of complications (0.6%) and in-hospital mortality (0.1%) [7].

Stereotactic radiation therapy has recently emerged as a safe and efficient therapeutic option for treating patients with refractory VT. Reliable and accurate navigation systems and radiation treatment planning adjusted to physiological movements of various anatomical structures (including chest motion, heart beatings, lung movements, etc) have ensured its rapid development and progress. Experimental and clinical studies have reported long-term effectiveness and safety of stereotactic radiation therapy for treating tachyarrhythmias [8]. This clinical case reports the first in-human stereotactic radioablation of ventricular arrhythmia refractory to medication and catheter ablation in the Russian Federation.

A 57-year-old patient with persistent VT was referred to stereotactic radioablation. The patient was admitted in the hospital in 2005 for acute MI and underwent balloon angioplasty of the right coronary artery (RCA). In 2007 the patient presented with multiple episodes of VT and VF interrupted by electrical impulse therapy. Amiodarone was started, but without any significant effect. In 2010 the patient underwent coronary angiography that reported an 80% stenosis of the RCA. Two stents were implanted in the RCA. In addition, the patient underwent RFA of the arrhythmogenic zones of the left ventricle (LV) using three-dimensional mapping of the LV anterobasal region and the interventricular septum at the edge of the scar tissue.

In 2017 the patient was admitted to the hospital with recurrent slow VT (110-140 bpm) on amiodarone. In 2018 RFA of VT was repeated using three-dimensional mapping of the left ventricular posterior septal region. A temporary effect was obtained, but in 2020 the patient was admitted with recurrent VT requiring the interruption with electrical impulse therapy (Fig. 1A).

In 2020 the patient was considered a candidate for stereotactic ablation. Three-dimensional activation map and voltage map were created using intraoperative non-invasive multichannel mapping for rapid verification of the tachycardia exit zone during its induction (Fig. 1 B,C). RFA was performed in the area of early activation in the anterolateral area of the left ventricle and in the area of late potentials and fragmented activity. However, tachycardia progressed with a transition to a faster one with unstable hemodynamics, requiring the interruption by external cardioversion. A single-chamber ICD with a remote monitoring and atrial signal sensing was implanted. The development of thyrotoxicosis required the withdrawal of amiodarone, resulting in an increase of VT burden. VT episodes were terminated by ICD antitachycardia pacing (ATP). Sotalol 160 mg per day was prescribed, but without any significant effects.

In 2022 the patient provided written informed consent to undergo stereotactic radioablation. The treatment planning algorithm consisting of 3 steps was developed to treat this patient: step 1 - preoperative management and planning; step 2 - stereotactic radioablation; step 3 - follow-up period.

Step 1 “Preoperative Planning”

Preoperative examinations included echocardiography (Echo), cardiac magnetic resonance imaging, coronary angiography, Biotronik Iforia 7 VR-T testing, and endocardial high-density mapping of the left ventricle.

Echo report (2022): LVEF of 49% according to Simpson's, end-diastolic volume (EDV) of 149ml, end-systolic volume (ESV) of 76ml. Enlarged left cavities of the heart (left atrium = 42×51mm), slightly enlarged right atrium (38×50mm). Moderate hypertrophy of the unaffected LV myocardium. Normal LV diastolic function. Basal and mid inferior LV segments showed hypokinesia. Moderate mitral regurgitation. Mild tricuspid regurgitation. No blood shunting. LV contractile function.

Cardiac magnetic resonance imaging report (2021): LVEF of 43%; stroke volume of 87.8 ml; cardiac output of 5.2 l/min; EDV of 202 ml; ESV of 114 ml, myocardial tissue density of 1.05 g/ml; end-diastolic dimension of 114 mm. Enlarged LV cavity. Inferior LV segments showed augmented contractility. Thinning of inferior LV segments. Myocardial thickness of less than 3 mm (reduced signal). Delayed contrast enhancement in the basal inferior, mid inferior, mid inferior basal, apical, and inferior segments of the LV. Left atrium of 44.5x74 mm, left atrial volume of 96.5 ml. Scarring of the basal inferior, mid inferior, mid inferior basal, and apical inferior segments after MI. Reduced left ventricular contractile function. Grade 1 mitral insufficiency (Fig. 3).

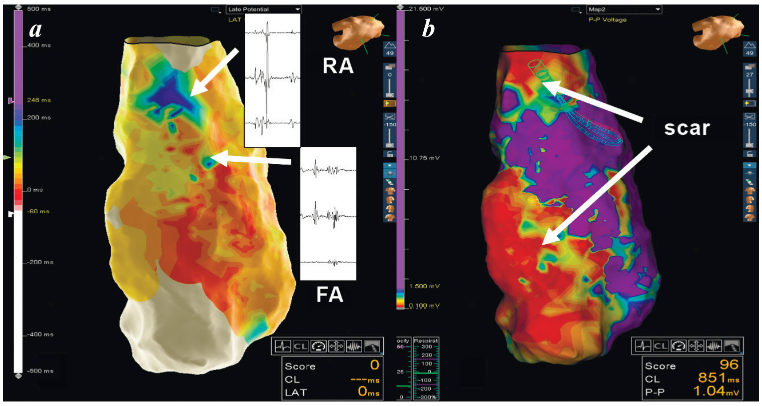

Fig. 2. High-density mapping of the left ventricle. a - a map of late potentials. b - voltage map in the signal amplitude ranging from 0.1 to 1.5 mV. Note: a - arrows show the registration of late potentials (LP), FA - fragmented activity; b - the arrow shows the red area with a minimum signal of less than 0.1 mV (the scar zone).

Coronary angiography (2021): right coronary blood supply. No signs of in-stent stenosis or thrombosis in the RCA.

Biotronik Iforia 7 VR-T testing report: VVI pacing rate of 40; Vs of 99%; ventricular pacing threshold of 0.6 V; lead impedance of 567 ohms; signal amplitude of 14mV; shock channel impedance of 80 ohm; pacing amplitude of 2.5V; pulse duration of 0.4 ms; atrial signal amplitude of 2.7 mV. The ventricular event detection parameters were as follows: VT 1 zone of 520 ms, VT 2 of 500 ms, VF of 300 ms; VT 1 - 1 ATP -7 ramps, VT 2 - 10 ramps, followed by 4-J and 8-J shocks. VF - 40-J shocks. Active VT-SMART detection algorithm. Twenty episodes of VT in zone 1, 160 - in zone 2 were registered since 2021. All were interrupted by ATP bursts. Battery charge - 100%, ICD battery voltage -3.21V.

Endocardial high-density mapping of the left ventricle was performed before stereotactic radioablation in the cath-lab. The interatrial septum was punctured to provide the access to the left ventricle. The multipole high-density grid catheter was passed through an introducer sheath. The Ensite mapping system was used to create the voltage map and activation map of the left ventricle. Voltage mapping revealed an extensive scar zone in the interventricular septum. There were areas of low-amplitude activity in the septal and apical segments of the left ventricle and areas of late potentials in the inferior basal and inferior septal segments of the left ventricle in the periscar zone (Fig. 2). Burst pacing was performed at a cycle length of 480-460 ms to determine re-entry tachycardia. It was located within the periscar zone. All findings were compared to define the target and radiation treatment planning for stereotactic radioablation (Fig. 3).

Step 2 "Stereotactic radioablation"

The fixing devices were developed to ensure accurate and reproducible patient positioning for topometric irradiation planning using computed tomography (CT). The patient was in the supine position with hands behind the head. The mattress was conformed to the patient's body and simultaneously hardened by evacuating the air with a vacuum pump. Abdominal compression was used to reduce diaphragmatic excursions (Fig. 4).

Four-dimensional (4D) CT imaging with 1.25 mm slice thickness of the region of interest (ROI) was performed. Native CT image series were obtained to mark the ROI and assess the degree of displacement of the heart chambers in one respiratory and cardiac cycle. Contrast-enhanced CT was performed to assess the heart anatomy and adjacent organs.

Contours of the target and adjacent critical structures were delineated on CT image sets each consisted of 10 fractions of the respiratory cycle. The contouring was performed in the Eclipse (Varian) treatment planning system allowing importing image sets obtained on various modalities and contour the target structures in various planes (axial, frontal, and sagittal). The target was located in the region of the interventricular septum and the apical inferior segment of the left ventricle according to the recommended 17-segment system. The gating of irradiation was carried out with the monitoring of the respiratory cycle. Therefore, the contour was delineated considering four phases corresponding to the exhalation. Each of the obtained contours represented gross target volumes (GTV) 1-4 (Gross Target Volume is the position and extent of the target visible in the images). The total volumetric value with the target in during the exhalation phase was delineated as GTVsum. The internal target volume (ITV) was generated from clinical target volume via application of 4 mm internal margins for possible inaccuracy of irradiation. Thus, the target encompassed all positions of the heart, taking into account its movement during the respiratory and cardiac cycles, as well as internal margins to address mechanical errors in dose delivery and patient positioning. In addition, the target, adjacent critical structures and normal tissues (esophagus, stomach, lungs, distal ICD electrode tip) were contoured.

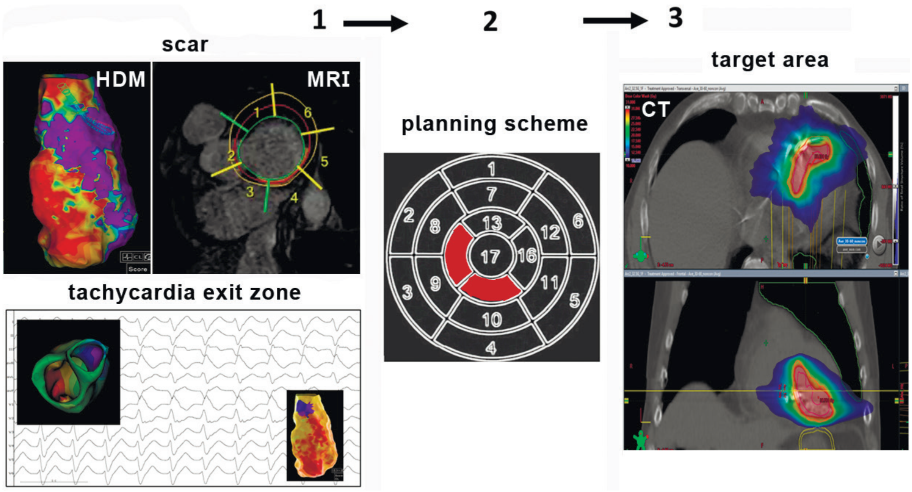

Fig. 3. Algorithm for planning the target area. 1 - collection of information about scarring and the tachycardia exit zone, 2 - schematic definition of the target area, 3 - projection of the target area in the left ventricle of the heart on computed tomography (native CT series) in the Eclipse radiation planning system. Note: HDM - high density mapping, CT - computed tomography, MRI - magnetic resonance tomography.

Fig. 4. Stereotactic ablation. Note: The position of the patient on the table of the True Beam Varian linear accelerator before radiation exposure. The figure shows a vacuum fixation mattress made individually for the patient with a special belt that restricts respiratory movements and a respiratory movement control sensor on the patient's chest.

Dose planning included the selection of optimal directions for dose delivery and the location of collimating devices. In addition, the inverse problem to optimize the dose distribution, taking into account the required dose in the target and normal tissues of the patient was solved (Fig. 3). The plan consisted of two full coplanar arches (the radiation source made two 360° turns around the patient in a plane perpendicular to the axis of his body). The main dosimetric characteristics are presented in Table 1.

Stereotactic radioablation was performed using the 6 MeV electron beam on a Varian TrueBeam linear electron accelerator (Fig. 4). Patient positioning was performed using cone beam CT, taking into account the patient's respiratory movements. 95% of ITV (46.8 cm3) and GTV (17.0 cm3) were dosed at 25 and 31.2 Gy, respectively. The patient was not sedated. Abdominal compression and fixation with a special bent were used to reduce diaphragmatic excursions. Breathing was controlled using a breathing monitoring system allowing performing radiotherapy during any phase of breathing (inspiration / exhalation/ breath-hold)). The procedure was performed under electrocardiographic control (Fig. 4).

Step 3 "Follow-Up Period"

The patient underwent the index procedure successfully. There were no adverse events within the in-hospital period. Postoperative daily ECG monitoring reported a decrease in the number of ventricular extrasystoles from 14,559 to 5,570 per day. There were no VT episodes registered within the in-hospital stay. Echo reported no signs of the pericardial effusion, LVEF of 49% according to Simpson's rule, EDV of 149 ml, and ESV of 76 ml.

The patient was discharged at day 7 after radioablation. The following medication therapy was prescribed: sotalol, rivaroxaban, gastroprotective drugs, and antihypertensive drugs. The patient received the schedule for follow-up to assess the long-term effectiveness and safety of the procedure, including regular visits, transthoracic echocardiography, chest CT, and gastroscopy. The ICD testing in the in-hospital period did not reveal any alterations in the ICD stimulation parameters from the baseline. None of VT episodes were registered. After discharge from the hospital, the patient was monitored remotely in ICD follow-up. Within 43 days after the index procedure, the incidence of VT paroxysms remained similar to the preoperative level (5 to 7 paroxysms of slow VT at a cycle length of 500-520 ms per week). All episodes were terminated by ATP. After that a gradual decrease in the number of paroxysms to 2-3 per week was observed. In the period from days 62 to 90, there were no VT paroxysms registered. The ICD parameters remained the same. The patient was continued to be monitored. ECHO-CG was performed in the period from days 30 to 90 and did not report any changes. There were no signs of pericardial effusion. By the end of the early follow-up period (90 days), the patient noted improved health and well-being.

DISCUSSION

The effective treatment of life-threatening ventricular arrhythmias with a high risk of SCD, including patients with reduced left ventricular pumping and contractile function and those with prior MI, remains an issue of concern in clinical cardiac electrophysiology. The most common mechanism causing sustained monomorphic VT in CAD patients is re-entry [9].

Catheter technologies for VT are constantly being improved. The accumulation of experience and the number of successfully treated patients with life-threatening VT has led to improved clinical outcomes and treatment safety [10]. However, some patients remain refractory to medication and catheter treatment or have significant contraindications to conventional ablation. All that emphasizes the necessity to develop new technologies that may improve the safety and efficacy of VT ablation, e.g. non-invasive stereotactic radioablation.

Recently stereotactic radiotherapy of malignant foci using medical linear accelerators and heavy charged particles has become a promising modality for treating oncology (particularly CNS tumours). Novel technologies allow shaping the high-dose radiation beam to conform to the target volumes with high precision and selectivity. The delivery of conformal radiation minimizes the radiation exposure on the adjacent healthy tissues and minimizes acute and delayed radiation complications [11]. Non-invasive stereotactic treatment using linear electron accelerators can be considered as a promising alternative to catheter ablation in patients with refractory tachyarrhythmias.

The pre-clinical studies have formed the evidence base for stereotactic radioablation that is now used for developing protocols for treating tachyarrhythmias in the clinical settings. The most developed area for stereotactic radioblation is the treatment of ventricular arrhythmias [12].

In our recent experimental animal study, we have demonstrated efficacy and safety of stereotactic radioablation for creating persistent myocardial damage. The results of macro- and microscopic examination showed significant changes in the target zones. These areas had precise but uneven damage boundaries, which were within the planned ones (conformal exposure with a high degree of precision) [13]. Obtained results ensured the translation of stereotactic radioablation in the clinical practice with the first in-human treatment in Russia.

This clinical case is the first in-human treatment of refractory VT in our country using a linear particle accelerator. There are over 10 recruiting clinical trials globally with the total study cohort of 250 patients. The first studies of

Table 1.

Main dosimetric characteristics

Parameters	V, cm^3	$D_{95\%}/D_{5\%}/D_{5cm^3}$, Gy	D_{mean}, Gy	D_{max}, Gy
GTVsum	17.0	31.3	34.2	40.1
ITV	46.8	25.0	31.5	40.1
Stomach	91.8	8.0 (<17.4)	2.4	20.2 (<22)
Stomach + 2 mm	115.1	10.9 (<17.4)	3.0	24.8 (>22)
ICD electrode tip*	1.3	20.3	18.4	21.8

Note: * - the distal part of the shock electrode of the cardioverter-defibrillator.

stereotactic radioablation have shown its effectiveness and safety. Obtained evidence has proved its beneficial potential for treating patients with VT refractory to medication and catheter ablation, regular ICD shocks, low LVEF, and those present with comorbidities or limited surgical access. Although several studies have reported the absence of any effects of radioablation in the long-term follow-up [10, 12].

The ENCORE VT trial has shown a decrease in the number of ventricular extrasystoles and VT episodes in 17 patients out of 18 (one death was not associated with the procedure). Robinson et al. reported 94% suppression of VT (the preoperative incidence of VT episodes was 119 versus 3 VT episodes within the 6-months follow-up after the index procedure) [12]. The average number of ICD therapies decreased from 4 before ablation to zero after it. Patients with arrhythmogenic PVC-induced cardiomyopathy demonstrated a decrease in 24-hours PVC burden from 24% to 2%. Patients experienced an absolute LVEF increase of 13%. Eleven patients in the VT group (69%) had VT recurrence within 6 months. Overall patient survival was 89% at 6 months and 72% at 12 months [10, 12].

However, certain complications associated with stereotactic radioablation have been described. One patient experienced pericarditis, two patients – radiation pneumonia, and five patients – hemodynamically insignificant pericardial effusion. In all cases, the therapy provided positive results [12]. The literature review has not reported any cases of functional damage to the electrodes and implantable devices during exposure and in the long-term follow-up. However, cooling (reducing the exposure dose when planning the procedure) of the distal ICD electrode tip is reasonable as radiation might lead to the damage of the contact with the myocardium, resulting in alterations of ICD stimulation and detection.

The ENCORE VT trial has shown a significant reduction in the number of VT episodes, antiarrhythmic therapy, minor cases of complications associated with the procedure, as well as improved quality of life. Our results reported in this clinical case are consistent with previously reported findings. We observed a 4-fold decrease in the number of ventricular extrasystoles within the in-hospital stay and short-term follow-up. There were no VT paroxysms within 62 days after the index procedure. The patient underwent radioablation procedure successfully without any complications.

However, the widespread use of stereotactic radioablation in routine clinical practice is currently limited by the lack of results obtained in randomized and large-scale clinical trials (current study cohorts does not exceed 30 patients), the complexity of preoperative patient management, the definition of indications and the protocol for managing and monitoring the patient, as well as high cost of the procedure and equipment [10, 12, 13]. To ensure successful and safe radiosurgical therapy, a multidisciplinary team, including an interventional cardiologist, a cardiologist, a cardiac surgeon, a radiotherapist, an anesthesiologist, and a medical physicist, should be introduced. Nevertheless, we conclude that non-invasive stereotactic radioablation is a novel promising treatment modality for refractory VT.

CONCLUSION

This clinical case demonstrated short-term efficacy and safety of stereotactic radioablation for ventricular tachyarrhythmias. Comprehensive management of patients with VT is based on a holistic approach, in which stereotactic radioablation should be considered as one of the methods for treating patients with VT refractory to medication and ablation treatment. Clinical outcomes depend on the accurate selection of patients and effective planning for radioablation therapy.

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